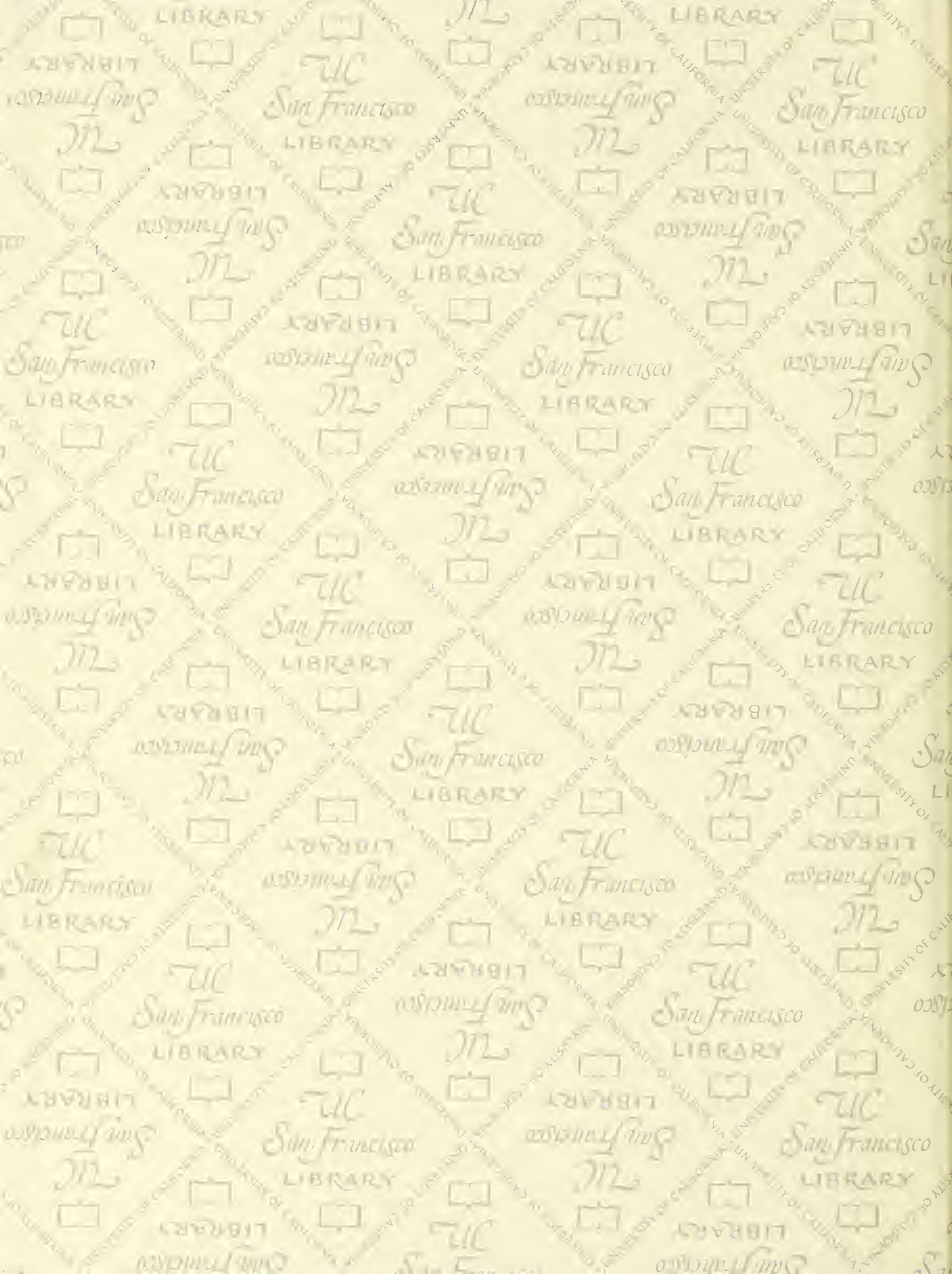
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for doctors and their patients

Official Journal of the NORTH CAROLINA MEDICAL SOCIETY January 1985, Volume 46, Number 1

Common Mononeuropathies, page 7

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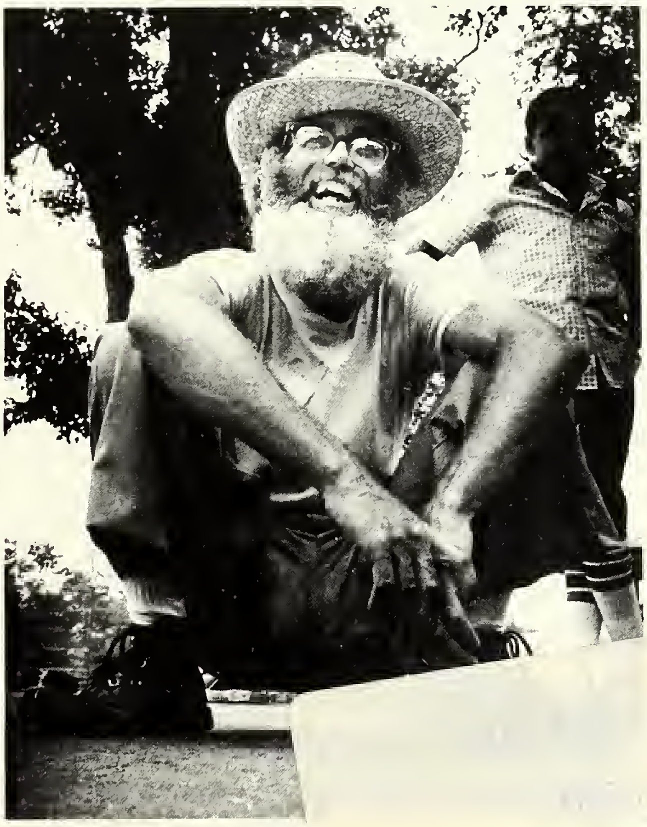

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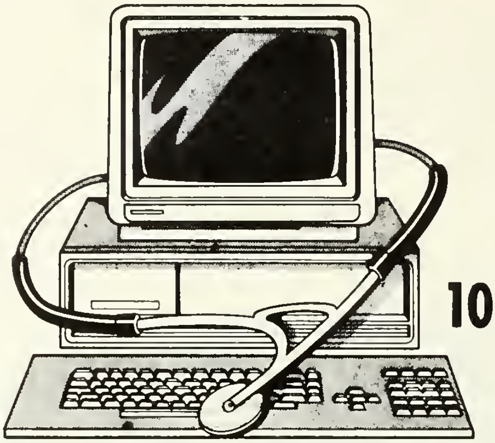

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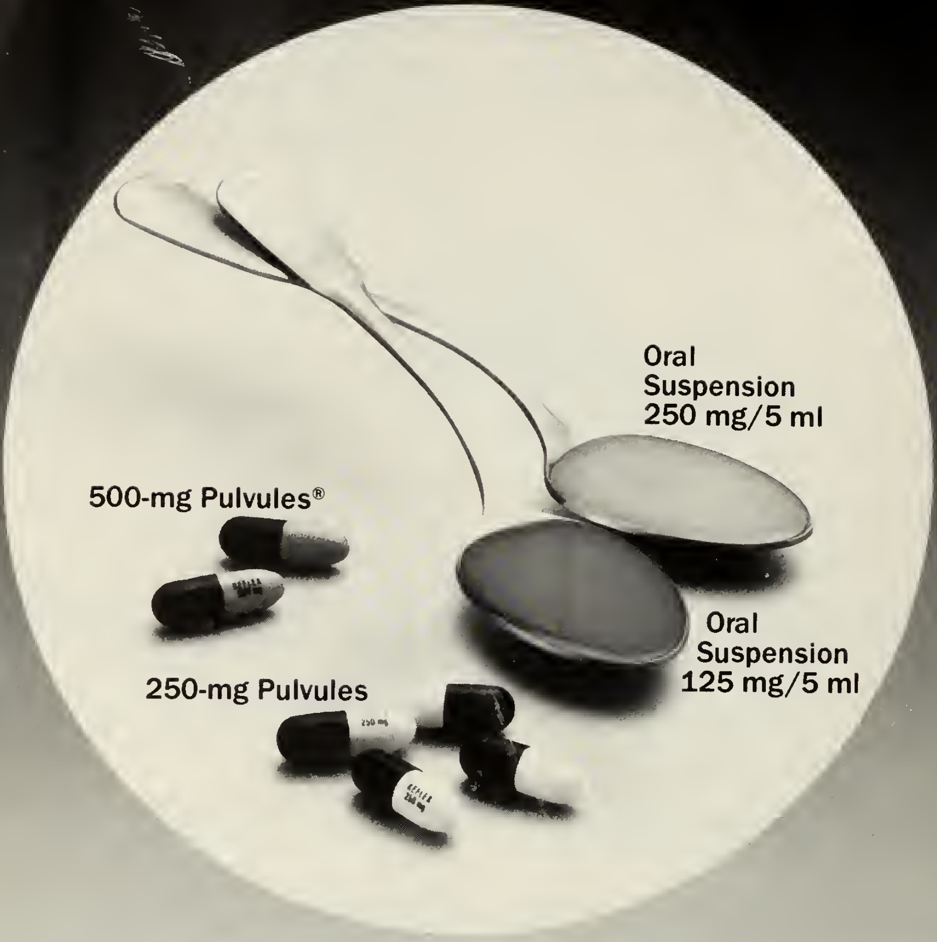

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SCIENTIFIC ARTICLE

Common Mononeuropathies

E. Wayne Massey, M.D.

• *A brief guide to the causes and cures of most common mononeuropathies.*

MOST mononeuropathies seen by physicians are "non-traumatic" in origin and due to nerve entrapment at various articulation points.

Median Nerve (Plate I)

1. Signs and Symptoms

The most common chronic mononeuropathy is the carpal tunnel syndrome (CTS). This very common neuropathy begins with intermittent numbness and tingling in the fingers, usually worse at night or when using the affected hand. The syndrome is more common in the dominant hand and symptoms are accentuated by writing, knitting, driving, bowling or similar exercise of the right hand. The diagnosis of entrapment at the wrist is often obscured by the wide distribution of pain to points distant from the site of the lesion: aching in the forearm or even shoulder which may exceed the severity of local hand symptoms. The patient loses agility and strength in the intrinsic hand muscles supplied by the distal branch of the median nerve (first and second lumbricals, abductor pollicis brevis, opponens pollicis, and the superficial belly of the flexor pollicis brevis) resulting in inability to use the hand for such tasks as opening jars or bottles. Sensory symptoms may confuse the physician because they may not be localized only to the classical median side of the hands. This may be because of the patient's inaccurate reporting, because of the sensory overlap of peripheral nerves, or because of variation in the dermatomal distribution in the median nerve.

Signs of the CTS may be subtle and only detected when the physician has a high degree of suspicion. Atrophy and weakness of the lateral thenar muscles may be signs of motor denervation (figure 1). The hand may appear bruised and have decreased autonomic function, particularly sweating. There may be decreased pain and touch perception in the first three digits and the radial surface of the fourth digit. Tinel's sign, radiation of paresthesias distally in the distribution of the median nerve with percussion over the flexor retinaculum at the wrists, and Phalen's sign, reproduction of paresthesias in the distribution of the median nerve with forced flexion of both wrists, may be helpful in diagnosis.

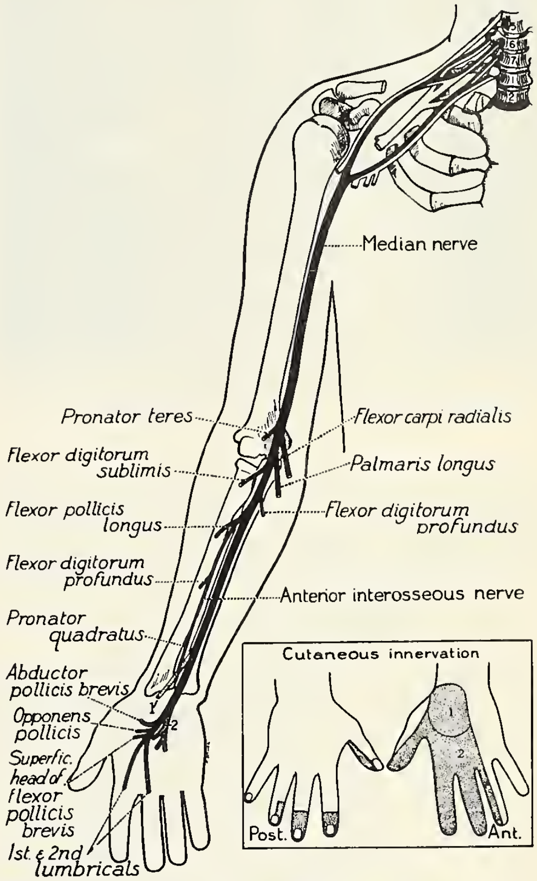

Plate I. *Median Nerve Supply*

2. Diagnostic Procedures

Nerve conduction studies demonstrating normal conduction velocities but a delay in either motor or sensory latency (or both) confirm the diagnosis of CTS at the wrist. Electromyography may demonstrate high voltage polyphasic motor units, which are the signs of chronic denervation, and fibrillations, a sign of acute denervation. In early CTS, however, the only abnormality on an electromyogram may be a diminished number of recruitable motor units.

3. Etiologies

The underlying processes responsible for CTS may include compression of the median nerve due to swelling in

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From the Division of Neurology, Department of Medicine, Duke University Medical Center, Durham 27710.

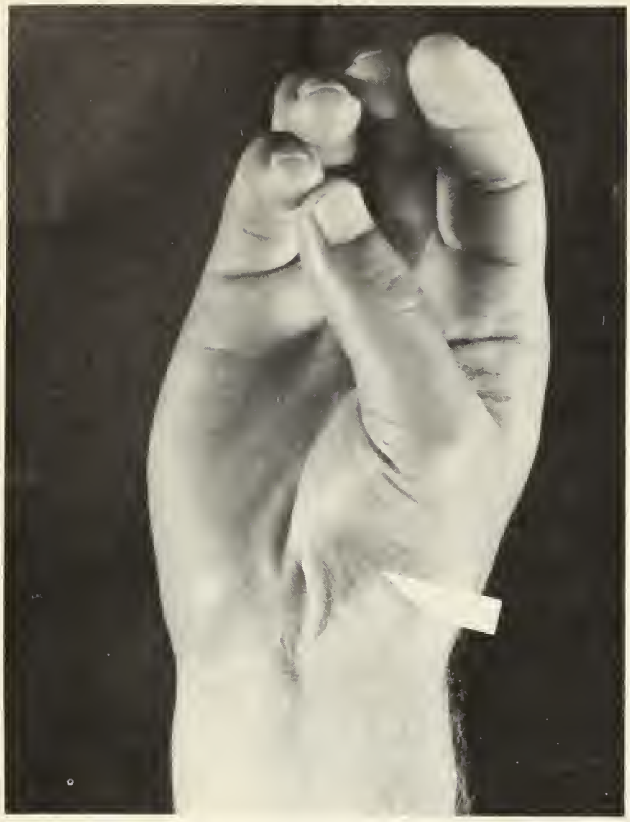

Figure 1. *Median nerve entrapment underneath transverse carpal ligament; thenar muscle atrophy is present.*

the carpal tunnel caused by pregnancy,[1] rheumatoid arthritis,[2] tenosynovitis,[3] gout,[3] myxedema,[4] acromegaly,[5] diabetes mellitus,[6] trauma, or amyloid.[7] Most often, however, no specific underlying disease can be identified.

4. Other Locations for Involvement

The median nerve may be injured proximally, as it dives through the pronator teres muscle, to course distally in the forearm. In this syndrome the sensory distribution is identical to that of CTS, but the weakness includes the pronator teres, the flexor digitorum superficialis, and the section of flexor digitorum profundus to the second and third digits of the hand. The "pronator teres syndrome"[8] causes weakness of flexion of most of the digits and hand but preserves ulnar flexion and deep strength of grip supplied by the ulnar portion of flexor digitorum profundus in the powerful fourth and fifth digits.

Another injury point for the median nerve is distal to its division point under the pronator teres muscle, at the origin of the anterior interosseous branch. This deep branch may be injured while the distal superficial median nerve is unaffected so that sensation and thenar muscle strength may be preserved. Weakness occurs in the flexor digitorum profundus radialis, which affects terminal flexion of the second and third digit, and in the flexor pollicis longus which causes flexion of the tip of the thumb. This injury renders the patient unable to make a circle "O" sign in the affected hand, a movement critical for pinching activity, for grasping very small objects, and for performing many fine movements which use opposition of tips of thumb and index finger.

5. Treatment

Treatment of CTS includes a) wrist splinting using firm support to the wrist to discourage flexion/extension, b) local steroid injection under the ligament, or, most often, c) surgical section of the transverse carpal ligament.

Ulnar Nerve (Plate II)

1. Symptoms and Signs

Ulnar nerve entrapment produces numbness of the fifth finger and the ulnar surface of the fourth. Weakness of grip, opening jars, and finger spreading may be noticed since most of the intrinsic hand muscles are supplied by the ulnar nerve: all of the muscles of the hypothenar group, all of the dorsal interosseous muscles (including the large muscle between the thumb and index finger), and the third and fourth lumbricals. The greatest strength in the grip usually is supplied by the ulnar-innervated half of the flexor digitorum profundus. On examination, atrophy and weakness of the abductors and the dorsal interossei may be evident (figure 2). Palpation of the ulnar nerve in the olecranon notch may demonstrate an enlarged and easily palpable nerve (and neuroma can form in this canal).[9]

2. Etiology

Entrapment injury to the ulnar nerve is common in

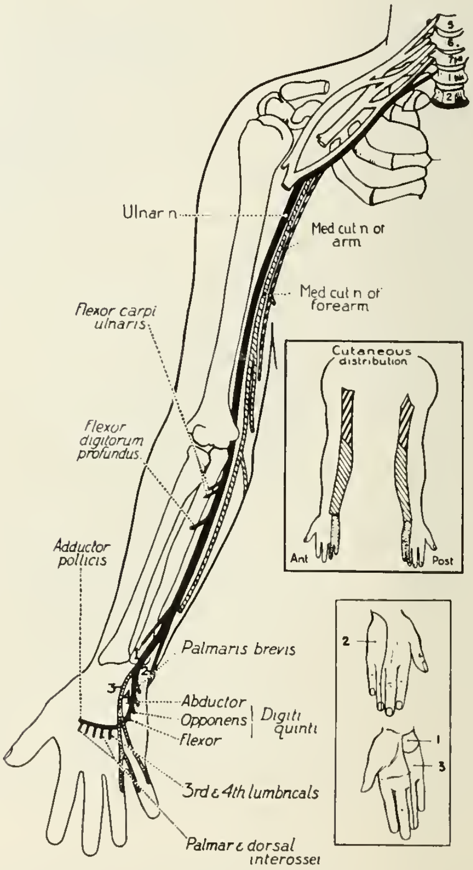

Plate II. *Ulnar Nerve Supply*

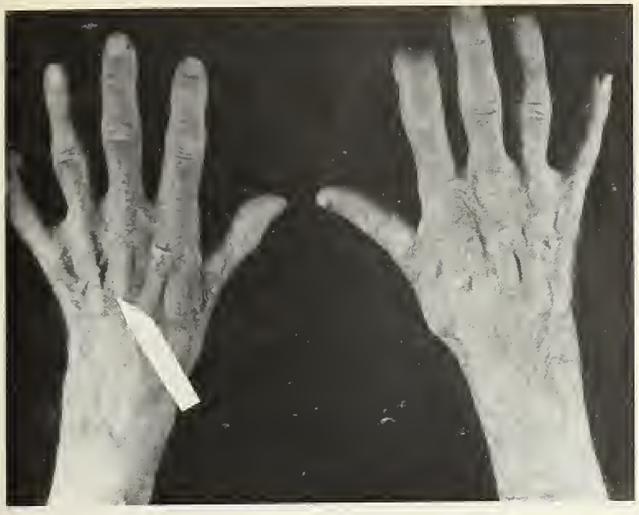

Figure 2. *Atrophy of interossei muscles due to chronic ulnar compression.*

chronic illness. Patients who are restricted to bed or a wheel chair on which they may place their elbows for support often entrap the ulnar nerve at the olecranon notch ("tardy ulnar palsy"). The immobile supine position, with the arms in a position of mild flexion and the forearm pronated, exposes the ulnar nerve to chronic pressure. Injury of the ulnar nerve can also result from occupational or athletic movements of simultaneous flexion-extension and supination-pronation movements such as holding rifles, shoveling, and throwing.

3. Diagnostic Aids

Slowing of nerve conduction velocity or drop in amplitude across the elbow supports the clinical diagnosis.

4. Other Locations

The ulnar nerve can be trapped in several other locations which cause characteristic clinical deficits.[10] A lesion low in the forearm, but still proximal to the sensory branch preserves function of the more proximal branches feeding the flexor digitorum profundus; only ulnar sensory deficit and weak intrinsic hand muscles result. When the superficial distal branch of the ulnar nerve is injured, only sensory loss in the ulnar distribution (which does not supply the forearm but only the ulnar surface of the hand) is present without motor loss; an unusual injury. The more common "jackhammer palsy" is caused by damage to the ramus profundus (deep branch) of the ulnar nerve in the hand. Injury to this branch in the palm, distal to origin of the sensory branch which takes off in the wrist, produces no sensory loss at all. Strength in the hypothenar muscles, abductor digiti quinti and opponens digiti quinti is intact; the only muscles affected are the third and fourth lumbricals and the dorsal interossei. Atrophy of the intrinsic hand muscles, loss of dexterity of all the fingers, inability to spread the fingers, and obvious weakness of the hand result. Nerve conduction may be normal if the evoked response is measured only in the (spared) hypothenar muscles, but if evoked response is performed from the ulnar nerve to the first dorsal interosseous, or if EMG is performed upon the interossei, the abnormality will be detectable.

5. Treatment

Avoidance of elbow pressure is the primary treatment. Flexor surface transfer of the nerve is required only when signs are severe.

Radial Nerve (Plate III)

1. Symptoms and Signs

The hallmark motor deficit of radial nerve palsy is wrist drop (figure 3). Since extension of the wrist is necessary for useful grip and finger flexion, the hand is rendered essentially useless, and it may paradoxically appear that there is weakness of finger flexions. The patient may complain of weakness in grip but when the hand is held in extension all flexor functions are normal. The position of the injury can be localized by testing the triceps muscles. If the triceps muscle and reflex are affected, the damage is more proximal, such as that occurring from crutches.

It is important to distinguish a radial nerve injury from C_7 root injury. The brachioradialis muscle ($C_{5,\,6}$) and extensors of the wrist ($C_{7,\,8}$) are both supplied by the radial nerve. Muscles supplied by C_5 include the deltoid and the biceps; C_6 supplies the supra- and infraspinatus as well as the biceps but none of these muscles are supplied by the radial nerve. The radial nerve from its more proximal branches supplies the triceps muscle. The brachioradialis

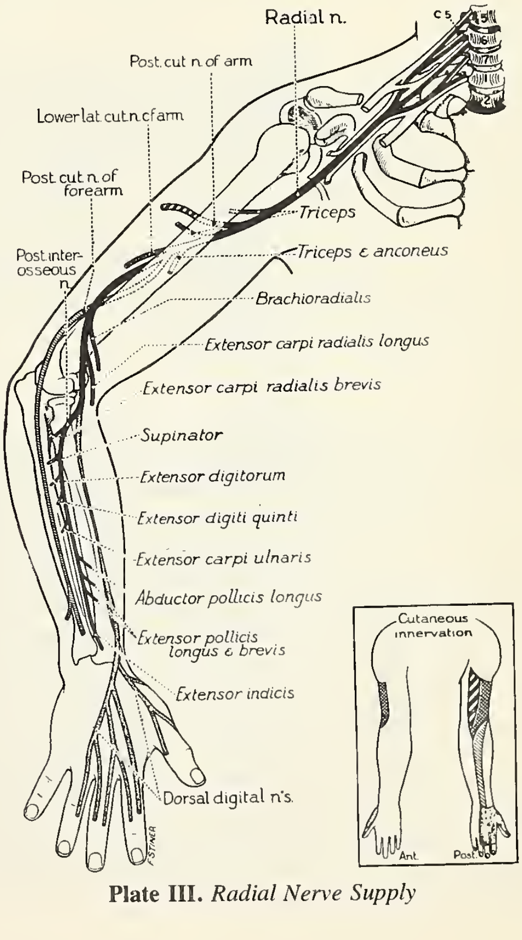

Plate III. *Radial Nerve Supply*

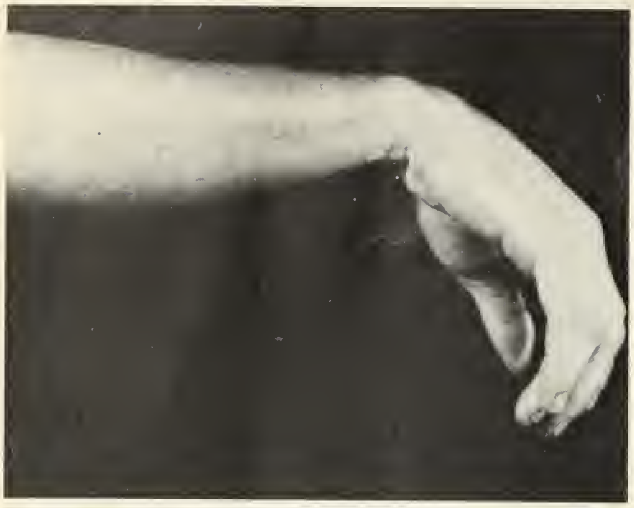

Figure 3. *Wrist drop from radial nerve entrapment.*

muscle ($C_{5,6}$) will be weak in a radial nerve palsy but spared in C_7 radiculopathy. This muscle is tested by evaluation of flexion of the elbow with the forearm midway between pronation and supination.

2. Diagnostic Aids

Nerve conduction velocity (NCV) of the superficial radial nerve and electromyography (EMG) of radial supplied muscles may assist when the clinical diagnosis is not clear. EMG changes begin to appear two to three weeks after the insult.

3. Etiologies

The most common site of injury of the radial nerve is in the proximal portion of the nerve as it wraps behind the humerus. This occurs while the patient is asleep or unconscious (usually due to alcohol) when the arm is held in abduction and lateral rotation against a sleeping partner lying with the head against the humerus (''honeymoon palsy''), or when the arm is propped over a bench, chair, or bar (''Saturday night palsy''). Usually there is no sensory loss, but when it occurs the involved area is the dorsal web between the thumb and the first finger.

4. Other Locations

Additional sites of radial nerve injury include the superficial sensory branch and the branch to the supinator muscles proximal and lateral in the forearm, the latter caused by: a) bursitic injury to the terminal supinator branch, or b) injury at the elbow causing distal trauma to the branch of the radial nerve supplying the muscles of supination: anconeus and the supinator. Involvement of these muscles causes weakness, and sometimes pain with pronation, and may be confused with ''tennis elbow,'' an articular tenosynovitis. Cheiralgia paresthetica,[11] the clinical syndrome of entrapment of the distal superficial radial nerve, may occur with strictures around the wrist, such as handcuffs, or such unsuspected sources as intravenous medication infiltration from the superficial vein over the radial surface (figure 4). This syndrome is entirely sensory causing burning, tingling, and numbness in the distribution of the sensory branch of the radial nerve.

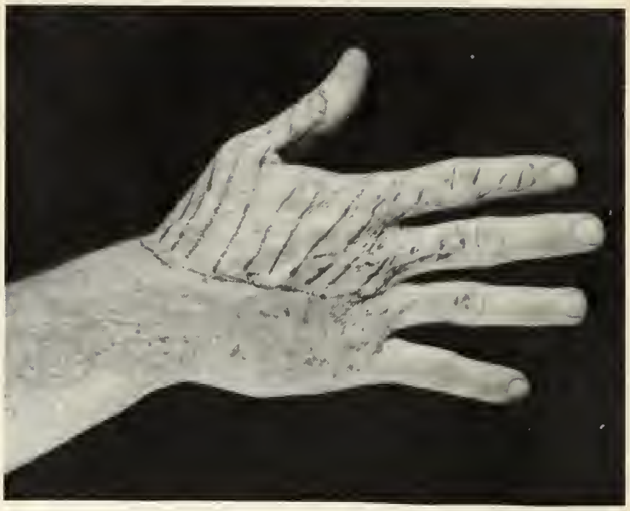

Figure 4. *Cheiralgia paresthetica due to superficial radial nerve lesion.*

5. Treatment

Treatment of radial nerve palsy consists of observation for six to eight weeks and avoidance of causative pressure. A ''cockup'' splint may assist hand function until it returns. Prognosis is usually good.

Lateral Femoral Cutaneous Nerve of Thigh

1. Signs and Symptoms

The lateral femoral cutaneous nerve, a sensory nerve

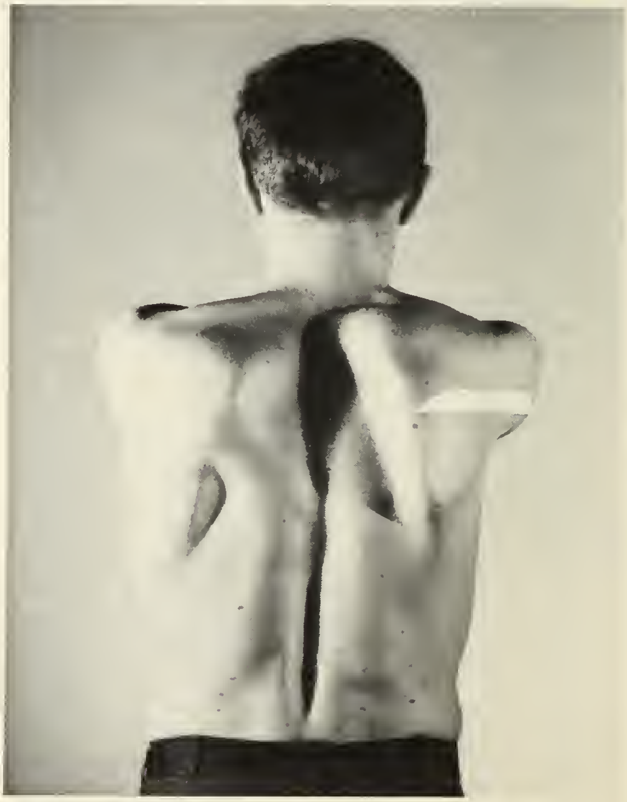

Figure 5. *Meralgia paresthetica from lateral cutaneous nerve injury with numbness and hyperesthesia.*

which arises from the lumbar plexus, may become entrapped at the inguinal ligament producing an acute or subacute onset of numbness and a disagreeable prickly sensation over the lateral thigh (meralgia paresthetica).[12] The disturbed sensation may be described as "burning," "pins and needles," or mere discomfort (figure 5). Surprisingly, this neuropathy is often not symptomatic and may, therefore, be detectable only by examination.

2. Diagnostic Aids

Recognition is important to avoid inappropriate intervention and to treat other conditions. Regretably, patients have been subjected to myelography and even to laminectomies for "repair" of this injury, when the anatomical deficit is clearly more peripheral. In the elderly, pelvic workup is essential since pelvic carcinoma may involve this nerve.

3. Etiology

There is a familial incidence of this neuropathy.[13] Causative factors include: standing at attention, playing sports (jogging), constrictive belts, and following surgical procedures. There is a high incidence among physicians[14] which is probably due to the simple convenience of evaluation of colleagues with this common neuropathy.

4. Treatment

Treatment, when symptoms warrant it, includes "neuropathic pain treatment" (amitriptyline, phenytoin, carbamazepine) or sometimes local nerve injection below the inguinal ligament and rarely section of the nerve.

Femoral Nerve (Plate IV)

1. Symptoms and Signs

Relatively uncommon, but devastating, is femoral neuropathy. Although usually of abrupt onset, the onset may be insidious as pain and numbness and later atrophy in the anteromedial thigh are noted. Severe weakness affects the iliopsoas and quadriceps muscles, with diminished or absent patellar reflex (figure 6).

Pain usually disappears within a few weeks, but the weakness may persist. Absence of radicular symptoms should eliminate an intervertebral "disc" diagnosis.

2. Diagnostic Aids

EMG showing acute denervation may help confirm the diagnosis. If compression of the femoral nerve by a pelvic mass is possible, CT scan of the lumbar plexus may assist in the diagnosis.

3. Etiology

Stretch of the femoral nerve may occur with leg hyperextension. In nontraumatic cases, 75 percent of patients with femoral neuropathy have diabetes mellitus. It may be the first indication of diabetes. In diabetes, the underlying cause is probably occlusion of the vasa nervorum.[15] Other etiologies include retroperitoneal mass, due to either neoplasm or hematoma (i.e., coagulopathy); periarteritis nodosa; femoral hernia; and gestational deliveries.

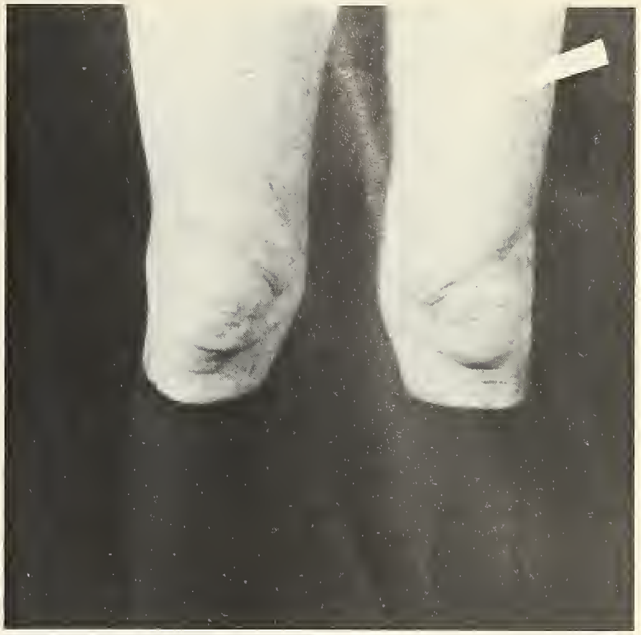

Figure 6. *Femoral neuropathy producing left thigh atrophy.*

4. Treatment

Treatment consists of physical therapy and pain relief.

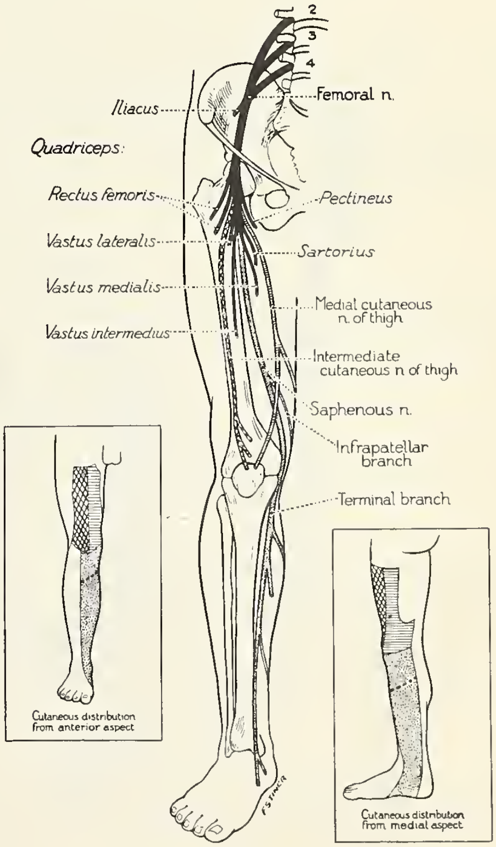

Plate IV. *Femoral Nerve Supply*

Peroneal Nerve (Plate V)

1. Symptoms and Signs

Peroneal nerve injury may cause footdrop or loss of sensation in the anterolateral surface of the foot. This can be subtle, with the only detectable sign being preferential wearing down of the anterolateral and toe portions of the shoe sole. Weakness of dorsiflexion and eversion of the foot and sensory loss in the anterolateral portion of the foot are important clinical signs. Weakness in the distribution of the peroneal nerve may be distinguished from that due to an L_5 lesion by the following observations: 1) The extensor digitorum brevis is supplied by the superficial peroneal nerve, but not the S_1 root. It may be weak (or atrophied) with peroneal nerve injury but not by L_5 root lesions. 2) The tibialis posterior muscle exerting plantar flexion and inversion of the foot is innervated by L_5 and S_1 roots but by the tibial nerve rather than the peroneal nerve.

2. Diagnostic Aids

EMG and NCV may help to determine the severity of the involvement and to distinguish peroneal from L_5 involvement.

3. Etiology

The most common inciting cause of common peroneal nerve injury is crossing the legs.[16] Observing a ''dimple'' sign overlying the fibular notch may give evidence of chronic leg crossing (figure 7). As with other entrapment neuropathies, immobility is a predisposing cause, and depression seems to predispose patients to peroneal neuropathy.[17] It is also seen post-stroke and in dementia. In addition to chronic leg crossing, trauma to the lateral surface of the knee, as during surgery, or trauma to the lateral surface of the leg (hence the name ''running board'' palsy) may produce this severe disability. Hunkering may cause this in North Carolina[18] (see cover illustration).

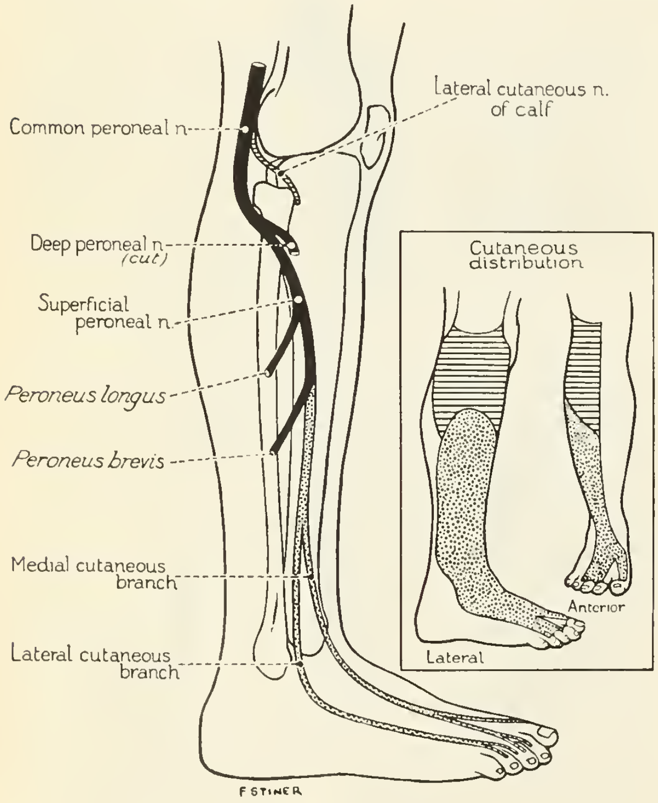

Plate V. *Peroneal Nerve Supply*

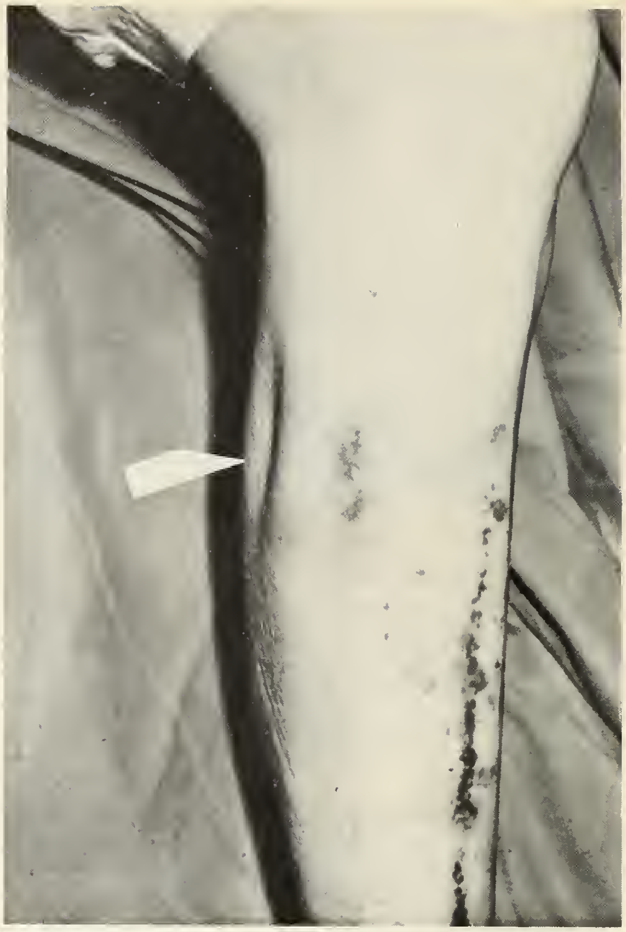

Figure 7. *Peroneal nerve palsy producing anterior compartment atrophy; note ''dimple'' at the fibular neck.*

4. Treatment

Treatment is aimed at avoidance of leg crossing or other repetitive trauma.

Sciatic Nerve (Plate VI)

1. Symptoms and Signs

Pain on raising the legs, numbness in the foot, radiating ''tingling'' or pain on movement are common symptoms. In addition to accurate motor and sensory testing of the extremity, examination of the skin (Herpes lesions or evidence of trauma) and local palpation along the course of the nerve are important.

2. Diagnostic Aids

EMG and myelography or CT scanning can assist in diagnosis.

3. Etiologies

''Sciatica'' is usually caused by a protruded lumbar disc

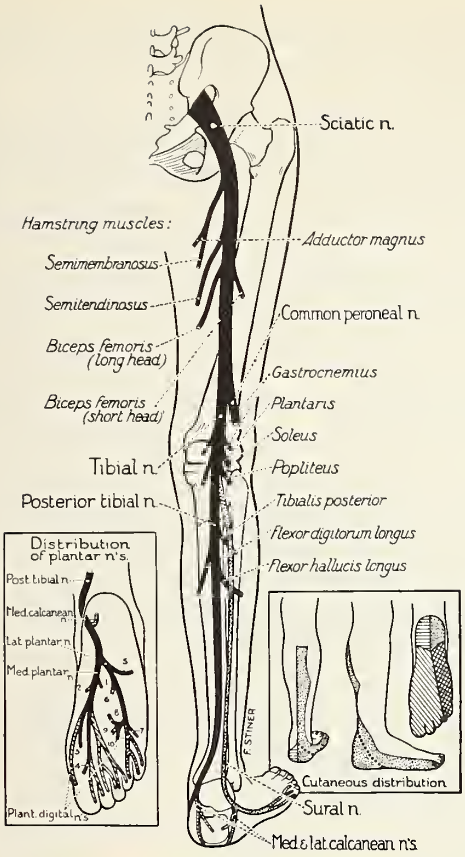

Plate VI. *Sciatic Nerve Supply*

affecting roots $L_{4,5}$ or S_1. However, the sciatic nerve is susceptible to injury at various sites in the buttocks area causing identical symptoms and signs. Local trauma to the buttocks area, such as pressure during surgery, excessive bicycle riding, wallet pressure, injections, and infections can injure the sciatic nerve in the buttocks.[19]

4. Treatment

If a disc is found by myelography it is usually removed surgically. However, conservative bed rest is often the initial therapy.

Brachial Plexus

1. Symptoms and Signs

Idiopathic inflammation of the brachial plexus (cryptogenic brachial plexopathy, Parsonage-Turner, neuralgic amyotrophy) predominantly affects the superior trunk of the brachial plexus.[20] A deep aching and pain in the axilla or shoulder is followed within a few days by weakness of muscles supplied by the superior brachial trunk, i.e., the supra- and infraspinatus, deltoid and biceps. Rhomboids, serratus anterior and other very proximal girdle muscles are sometimes involved, causing weakness of abduction and elevation of the shoulder, and weakness of external rotation (figure 8). The plexus may be affected in a spotty manner so that along with the predominant weakness of the muscles of the upper portion of the arm (Erb's palsy), muscles of the hand may also be weak.

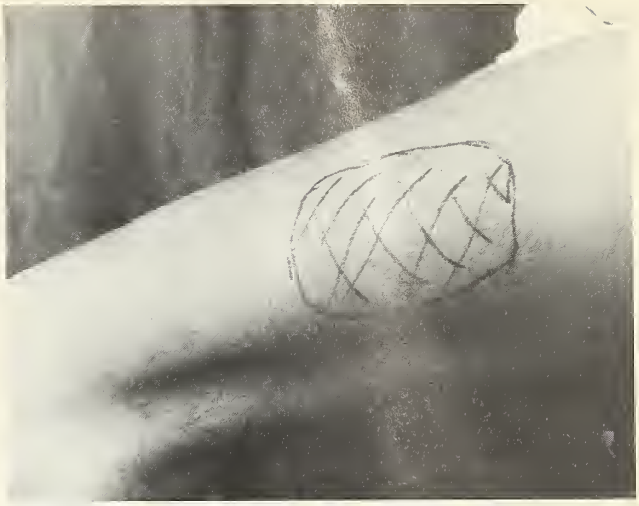

Figure 8. *Brachial plexopathy with focal weakness producing scapular winging.*

2. Diagnostic Aids

EMG may assist in localization several weeks after the onset of symptoms. Although shoulder pain is common, bursitis or cervical root injury can be distinguished from plexus lesions by virtue of the distribution of particular shoulder muscles, involvement of the rhomboid and serratus anterior, and relative paucity of sensory findings. Cervical spine, shoulder and chest x-rays are important to eliminate local disease or fractures.

3. Etiologies

Stretching or blunt trauma from automobile accidents or motorcycle accidents are common among adults. Carrying rifles or army rucksacks may cause stretching, especially of the superior trunk of the plexus.[21] Inflammatory plexopathy may be related to infection and to immunization; many cases have occurred after large-scale inoculations in the military.

4. Treatment

Treatment includes oral steroids, if painful, and physical therapy. Prognosis is excellent (80-90% improve).

Truncal Mononeuropathy

1. Symptoms and Signs

Localized truncal sensory loss is the primary sign.

2. Etiologies

Lumbar and thoracic radiculopathy is seen most commonly due to Herpes Zoster infection. Skin lesions are almost always present.

In diabetes mellitus, diabetic truncal mononeuropathy[22] occurs and may be at multiple levels.

3. Other Locations

Localized sensory loss on the back medial to the scapula at the T2-T6 spine level occurs with notalgia paresthetica[23] (Greek notos = back). This is very common and pruritis is frequent (figure 9).

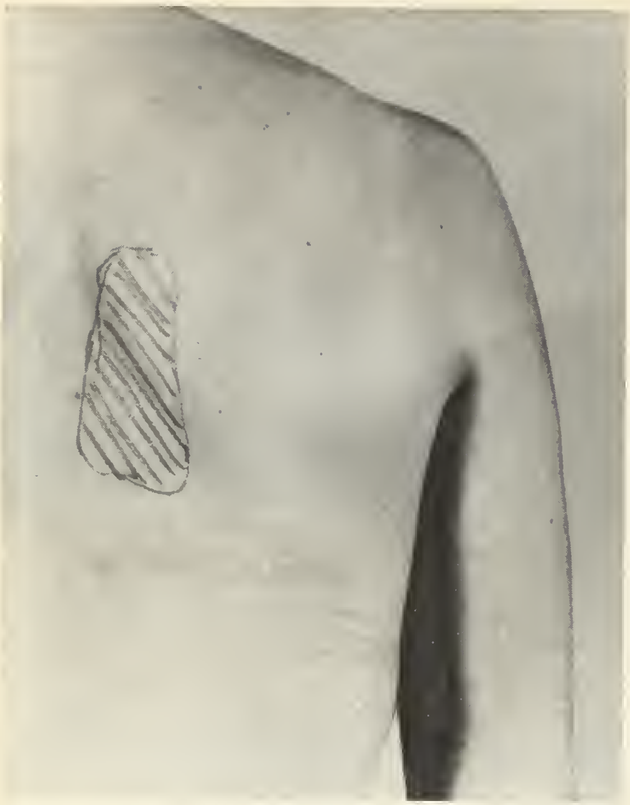

Figure 9. *Notalgia paresthetica. There is medial scapula sensory loss and pruritus.*

Peripheral Neuropathies Predispose to Mononeuropathies

Pressure neuropathies are more common among patients with the diffuse neuropathies: diabetes mellitus, chronic alcoholism, post-inflammatory neuropathy (Guillain-Barre) or metabolic dysfunction (thyroid, uremia, or hepatitis). Examples include peroneal palsy in the aged, CTS in myxedema, or ulnar neuropathy in patients recovering from Guillain-Barre syndrome. Physicians must be aware that patients with peripheral neuropathy are susceptible to secondary peripheral nerve injury.[24]

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SCIENTIFIC ARTICLE

The Management of Bee Hives

Stephen R. Nichols and Francis A. Neelon, M.D.

- *Do patients with exaggerated responses to insect stings need immunotherapy?*

THIS is the *North Carolina Medical Journal,* so we will not drone on about the intricacies of the apiary business, but will instead discuss the current medical management of insect sting reactions. We recently saw a young man in the clinic whose case history clearly illustrates the problems of caring for patients with bee stings.

A healthy 14-year-old boy came to the general medical clinic for evaluation. Twenty-six days ago he had suffered a generalized cutaneous reaction after being stung by a yellow jacket wasp and had come to the Emergency Room. He had been stung on his left ankle and within fifteen minutes his face and extremities were swollen and red; hives had sprung up on his chest, abdomen, and back; he itched a great deal. Thirty minutes later in the Emergency Room, the following observations were made: edema of the left axilla; truncal urticaria; clear lungs; and normal blood pressure and pulse, both of which remained stable. He denied any difficulty breathing or threatened loss of consciousness. He had been stung several times in the past with only a mild, localized response. He had no other allergies nor was there a family history of exaggerated responses to insect stings. He was not treated with epinephrine, but was given an anti-histamine by mouth for his urticaria and an Epi-Pen with instructions to carry it and to use it should he be restung. He was referred to the allergy clinic. In the outpatient clinic, the young man and his mother were concerned about the effectiveness, risks, and necessity of desensitization therapy.

We had only some vague ideas about the management of insect sting reactions on the level of "Refer to allergy clinic." After discussing the case with a couple of immunologists and following up their leads in the library,[1, 2] we found that only forty to fifty deaths a year are attributed to insect stings and that the vast majority (greater than 95%) of these are the result of allergic reactions rather than envenomation itself which requires literally hundreds of stings. It is important to stress that an allergic reaction to an insect sting is not an infrequent occurrence. Approximately 1 in 125-250 people who are stung will have a systemic allergic reaction. Surveys of the general population show that 1 in 25 individuals has had a systemic reaction at some time in the past; 1 in 5 will test as sensitive to at least one of the common insect venoms. What we learned in the library allowed us to appropriately interpret the patient's story and we re-present the case with clarifying comments below.

A healthy 14-year-old	A major point in the natural history and medical management of insect sting reactions is the marked difference between children and adults. More than 90% of insect-sting induced deaths occur in those over 20 years of age. In adults, 90% of systemic reactions are life-threatening, while in those less than 20 years of age only 30% of systemic reactions are so severe. It is presently recommended that all adults who have a systemic reaction to any degree should undergo desensitization therapy, but only those children who have already had a *life-threatening* reaction need such treatment.
boy	Two-thirds to three-fourths of individuals who suffer exaggerated responses to insect stings are male, but this represents increased exposure rather than sex differential susceptibility.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

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He denied any difficulty breathing or threatened loss of consciousness.

He had been stung several times in the past with only a mild, localized response.

Insect sting reactions can be categorized into two broad types: localized and generalized (table 1). The local reactions can be either the normal inflammatory response or an exaggeration of the normal response, both of which may have some mild, non-specific systemic symptoms (such as nausea, malaise, or headache) associated with them. The generalized reactions are allergic responses which can be limited to the skin (cutaneous) or can be potentially life-threatening (anaphylactic). Other types of allergic reactions occur, but are very rare.

Table 1: Definition of Insect Sting Reactions

I. Normal Local Reaction: redness and swelling in an area less than 2 inches in diameter with heat and pain that resolves in less than 24 hours.
II. Large Local Reaction: as for a Normal Local Reaction, except a greater area — up to an entire extremity — may be involved or resolution may take longer or both.
III. General Cutaneous Reaction: generalized erythema, angioedema, urticaria, pruritis.
IV. Life-Threatening Reaction: signs of laryngeal edema, bronchospasm, hypotension.

The insect order *Hymenoptera* contains several members (bees, yellow jackets, hornets, wasps, and fire ants) capable of causing the various reactions noted above. Only yellow jackets and hornets show considerable cross-reactivity and they are often grouped together as vespids, their family name. The prevalence of these insects varies geographically, with wasps and fire ants being more common in the temperate climate of the southern states.

Treatment of the reaction is imperative, especially if the reaction is serious, because 2 out of every 3 fatal outcomes from insect stings are associated with a complete lack of medical treatment.

More than 95% of non-fatal reactions occur within the first 30 minutes following the sting. There is evidence that a delay in the onset of reaction beyond 30 minutes is more likely in a fatal reaction.

These are the four basic characteristics of a general cutaneous reaction: angioedema; erythema; urticaria; and pruritus.

Elapsed time from sting to medical treatment totalled 45 minutes. *Prompt* medical treatment of the reaction is important since the elapsed time from the sting — not the reaction — to medical intervention is less than 60 minutes in 90% of serious but non-fatal reactions, whereas only 5% of fatal reactions are treated within 60 minutes of the sting.

Once again, the signs of a general cutaneous reaction.

There is no sign of bronchospasm or pulmonary edema, which are the cause of death in 70% of fatalities, and no indication of hypotension or shock. Combined, these observations indicate that this is not a life-threatening reaction.

These symptoms of cardio-respiratory embarrassment were denied; however, possible laryngeal symptoms (throat fullness or tickle, gagging or difficulty swallowing, or hoarseness or voice change) need to be assessed. Also, chest "tightness" may be the only symptom of bronchospasm.

This is commonly the case and there are no markers, at present, for predicting which individuals will or will not suffer a reaction of increased severity. However, there is good evidence that a change from a mild to more serious reaction does *not* indicate that progression to an even more serious reaction will occur. The rule of thumb is that the severity of the next reaction will be less than or the same as that of the most recent reaction. It is the exceptional case in which the reaction is worse.

He had no other allergies

Atopy is found no more frequently in those who have greater than normal reactions to insect stings than in the general population.

nor was there a family history of exaggerated responses to insect stings.

Such a family history is more common in anyone who has had an exaggerated response to an insect sting, but it is of uncertain significance.

He was not treated with epinephrine,

Epinephrine is the mainstay of treatment for the acute systemic reaction, but may not be necessary in mild systemic (cutaneous) reactions.

but was given an antihistamine by mouth for his urticaria

Anti-histamines are useful because they lessen the cutaneous response and relieve the pruritis, but they should only be considered after a decision regarding the use of epinephrine has been made and acted upon. The administration of anti-histamines should never delay institution of epinephrine treatment. For the management of all reactions, see table 2.

Table 2: Treatment of Insect Sting Reactions

I. Normal Local Reaction: cold compresses, elevation, non-steroidal anti-inflammatory agents.
II. Large Local Reaction: as for a Normal Local Reaction, plus anti-histamines by mouth.
III. General Cutaneous Reaction: epinephrine, anti-histamines, non-steroidal anti-inflammatory agents.
IV. Life-Threatening Reaction: oxygen and volume expanders — if necessary, epinephrine, anti-histamines, non-steroidal anti-inflammatory agents, aminophylline for prolonged bronchospasm and steroids for other significant, prolonged allergic responses.

and an Epi-Pen with instructions to carry it and to use it

An Epi-Pen is an auto-injector with a hidden needle that delivers 0.3 ml of 1 : 1000 aqueous epinephrine. The Epi-Pen is to be carried when the individual is in settings that provide increased risk of exposure to stinging insects.

should he be restung.

There is a two week period of anergy during which a person will not significantly react to a re-sting. However, 70% of children with systemic reactions are sensitive to more than one venom and could react to a sting by a different insect; on the contrary, 70% of adults are sensitive to only a single venom.

He was referred to the allergy clinic.

This aspect of the case is discussed at the end.

In the outpatient clinic, the young man and his mother were concerned about the effectiveness,

Whole insect extracts were once used in desensitizing vaccines, but are no better than placebo and have been replaced by the use of purified insect venoms. Venom immunotherapy is effective in 97% of cases or more, depending upon what maintenance dose is used.

risks,

Reactions are observed during the induction phase of immunotherapy, but rarely occur once the maintenance dose has been achieved. These reactions are usually not a great problem since they occur in the presence of a physician. Systemic cutaneous reactions that seldom require the use of epinephrine occur in less than 10% of patients, usually early in the induction regimen. Large local reactions occur in 20-25% of patients, usually later in the induction regimen.

and necessity

There is an important difference in the guidelines for managing adults and children by immunotherapy. All adults should have immunotherapy if they have had a systemic reaction and are skin test positive because there is a high likelihood that subsequent reactions will be systemic. In children, re-stinging only rarely produces reactions of increased severity; most show a decrease in symptoms. A prospective study[3] of children who had had large local reactions and no immunotherapy found that 60% of re-stings caused a normal response, 38% a large local reaction again, 1% a general cutaneous reaction, and 1% a life-threatening reaction. A similar study[4] in children with a general cutaneous reaction found that 90% of re-stings resulted in a local reaction; and 10%, a general cutaneous reaction; no life-threatening reactions were observed. This last study was particularly significant because some of the children were being treated with immunotherapy and some were not but no significant differences were found between the two groups in terms of the likelihood or severity of systemic reactions. Based on these studies, only children with life-threatening reactions and positive skin tests need to be treated with immunotherapy.

of desensitization therapy.

Another aspect of immunotherapy regards the duration of maintenance therapy. At present, this cannot be adequately addressed, but preliminary data suggest that it may be possible to discontinue therapy at some point — after several years — because the immune system tends to "forget" its sensitivity to insect venom with time, regardless of ongoing immunotherapy.

Table 3: Candidates for Immunotherapy

Adults: Everyone with any degree of systemic reaction and positive skin tests.
Children: Only those with a life-threatening reaction and positive skin tests.

The science of medically managing insect sting reactions is thus reviewed. However, there is some art involved in advising individuals who have suffered an insect sting reaction. The most perplexing cases are similar to the one presented: an adolescent with a systemic reaction that does not clearly warrant desensitization therapy. Our example demonstrates the problem of "common sense" precautions to reduce the chance of a re-sting (wearing shoes when outdoors and avoiding activity near trees and bushes or the use of attractants like canned drinks, perfumes, and bright clothing) because they often run contrary to the normal activities of an average adolescent. Recommendations to constantly carry an Epi-Pen are sound, but may not appeal to an adolescent. In addition, the psychological weight of the fear that the next sting "may be the last" can be so great, for the patients or the parents or both, that the patient's activities may become greatly, and unnecessarily, curtailed. These considerations need to be made individually and may require more than a narrow "scientific" perspective in order to achieve optimum medical management.

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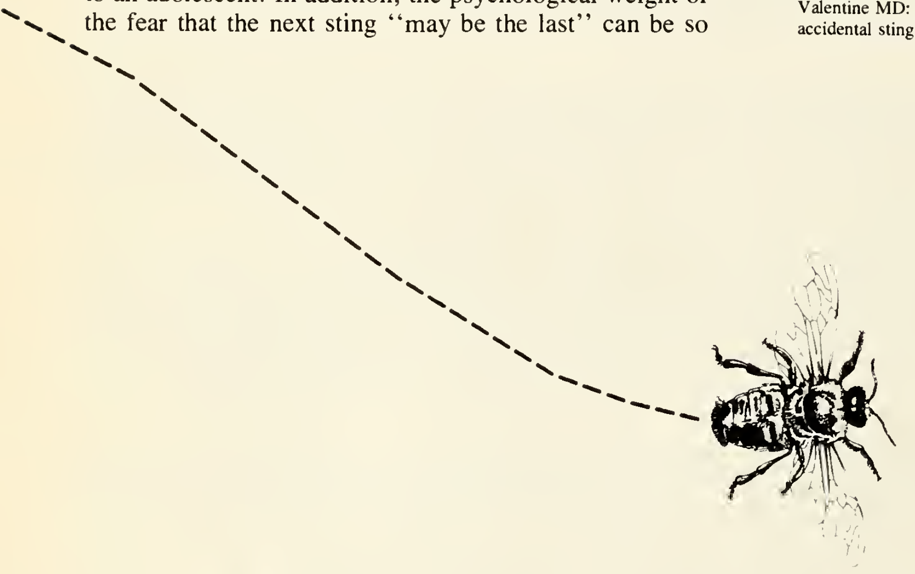

SCIENTIFIC ARTICLE

The Patient From Whom I Have Learned the Most: Undiagnosed Pulmonary Emboli Are Still With Us

Herbert A. Saltzman, M.D.

THREE disease processes in the same organ system present a challenge to the doctor. I was confronted with this challenge in January 1970 when a 60-year-old engineer pilot was admitted to my service. He enjoyed excellent health with a background of transient dyspnea during the preceding year and a negative detailed clinical workup including a chest x-ray in March 1969. In December 1969, however, the patient became incapacitated by dyspnea associated with wheezing and a productive cough. A workup elsewhere revealed a paralyzed right hemidiaphragm and bronchitis. Additional studies, including bronchoscopy and gastrointestinal x-rays, were unrevealing. The past medical history was positive for allergies to penicillin and sulfa and for variable rhinitis symptoms.

Significant physical abnormalities at admission to Duke included tachypnea, shallow respirations, use of the accessory neck muscles during respiration, diffuse wheezing over both lungs, tachycardia and trace pedal edema. Admission laboratory findings included leukocytosis with a shift to the left, normal mouth flora in a sputum culture, a paralyzed right hemidiaphragm by chest fluoroscopy, ventilatory obstruction (FEV1 0.9 L — 30%, FVC 1.58 L — 39%, maximal mid-expiratory flow rate 0.41 L/sec — 13%) and a compensated respiratory acidosis with hypoxemia (PaO_2 56 and $PaCO_2$ 46 mmHg, pHa $>$ 7.39).

The initial workup including bronchoscopy, and multiple cytopathologic studies of sputum failed to reveal evidence of malignancy. The hemidiaphragmatic paralysis was presumed to be idiopathic. Vigorous treatment with bronchodilators, physical therapy and broad spectrum antibiotics including tetracycline failed to relieve the profound dyspnea, and the sputum remained infected in character. During the second week of hospitalization a Hemophilus influenza organism, isolated from an endotracheal aspirate, proved resistant to ampicillin and tetracycline but susceptible to Chloramphenicol. A 10-day course was associated with a dramatic diminution of cough, sputum production and wheezing. Despite these favorable changes in the manifestations of bronchitis the patient remained profoundly dyspneic. There were no cardiac, metabolic, hematologic or neuromuscular causes for profound dyspnea, the lungs remained clear of infiltrates and the paralyzed hemidiaphragm could not explain continuing severe dyspnea at rest. For that reason the pulmonary vascular compartment was investigated by means of pulmonary arteriography. (The perfusion scan diagnostic methodologies of that era were not regarded as being diagnostically useful by many pulmonary physicians, including myself, in a setting of variable airway obstruction.) The pulmonary angiogram revealed in both lungs multiple filling defects considered diagnostic of pulmonary emboli. The patient was placed on intravenous heparin therapy. Remarkable improvement ensued with resolution of dyspnea and the residual wheezing. Of related interest was the failure of vascular contrast studies to identify a site of origin for the emboli within the deep veins of the lower extremities and inferior vena cava.

The patient was discharged essentially free of dyspnea or significant other pulmonary symptoms. He took an oral anticoagulant for six months. In ensuing years, right hemidiaphragmatic function substantially returned spontaneously, as judged by fluoroscopic followup. Intermittently he continued to be troubled by rhinitis and asthmatic bronchitis symptoms. These manifestations were treated conventionally.

The solution to this man's clinical illness depended upon recognition that unexplained clinical findings need to be pursued vigorously. The emphasis here is on the clinical findings. This patient had been very vigorous physically without difficulty until the time of the acute illness, except for a transient earlier manifestation of reactive airway disease. At the beginning of his acute illness the finding of hemidiaphragmatic paralysis, wheezing and dyspnea was presumed to reflect the consequences of a bronchogenic carcinoma with obstruction of the airway and invasion of the phrenic nerve by tumor cells. When the diagnosis of bronchogenic malignancy was rejected, on the basis of two independent and complete assessments in different hospitals, the problem of continuing dyspnea and wheezing could still be explained on the basis of superimposed infection in an individual with hyperreactive airways. While initial treatment of a conventional type failed to relieve the clinical manifestations of bronchitis, the identification of a resistant Hemophilus influenza organism in the airway did

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lead to well-directed antibiotic therapy that was clearly effective in controlling wheezing and sputum production. Yet the dyspnea persisted. At this point the clinician had to decide whether this persistent symptom could be explained by the combination of hemidiaphragmatic paralysis and residual obstructive airway disease. Paralysis of the hemidiaphragm, of itself, is not a cause of dyspnea at rest or even with ordinary activity in otherwise healthy individuals and at that point in the clinical course wheezing had essentially cleared. For that reason I did elect to pursue other possible explanations. There were no cardiac, metabolic, hematologic or systemic neuromuscular problems to explain dyspnea. Lung parenchyma was uninvolved by x-ray. Only pulmonary vascular disease remained unexplored as relevant to continuing dyspnea. Happily for the patient, pulmonary angiography identified the occult major cause of dyspnea and subsequent therapy was very successful.

Even in our modern era the diagnosis of acute pulmonary embolism is difficult.[1] In our hospital approximately half of the patients having an acute pulmonary embolism by angiography have VQ scan interpretations other than high probability.[2] Accordingly, those patients with low, indeterminate and intermediate readings, in the absence of a decision to do angiography, may well not be treated for their serious medical problem with a resultant higher morbidity and mortality. In that same population of patients, approximately 15% with high probability scans pursued to angiography failed to demonstrate pulmonary emboli. That group of patients, if not pursued to angiography, may for the most part have received anticoagulant therapy inappropriately with a resultant risk of morbidity and mortality that should not have occurred. These considerations should serve to keep the physician humble about his ability to make consistently accurate diagnoses of the presence or absence of acute pulmonary embolism. Improving diagnostic technologies in the future may help solve the problem.[3-5] A rigorously controlled prospective investigation of how to diagnose acute pulmonary embolism, sponsored by the National Heart, Lung and Blood Institute, will begin this year. The information to be provided by that experiment, we hope, will make diagnostic decision making a simpler task in the future.

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SCIENTIFIC ARTICLE

Spontaneous Pneumomediastinum: A Report of 10 Cases and Review of the Literature

Alan K. Halperin, M.D. and Richard E. Deichmann, M.D.

• *A review of cases, causes and treatment of a rare malady which occurs most often in young people.*

PNEUMOMEDIASTINUM, also termed mediastinal emphysema, can be defined as the presence of free air in the mediastinum. It was first described as a clinical entity by Laennec in 1819 as "interlobular emphysema." Laennec astutely observed that the "affectation is characterized by infiltration of air between lobules of the lung. . . . When extravasation exists near the root of the lungs, it speedily extends to the mediastinum, and from thence crosses to the neck and over the whole subcutaneous and intermuscular cellular substance of the body."[1] It remained a poorly recognized entity until 1939 when Hamman presented seven cases of spontaneous pneumomediastinum characterized by the unique precordial crunching sound which now bears the name "Hamman's sign."[2] Spontaneous pneumomediastinum develops inconspicuously secondary to alveolar rupture in patients with no serious underlying pulmonary disease.[3] It is distinct from traumatic pneumomediastinum in which air gains entry into the mediastinum by means of structures other than the alveolus, i.e., esophageal perforation, tracheobronchial tears, surgical procedures, or mechanical ventilation. Familiarity with pneumomediastinum is important because it must be differentiated from other more serious causes of chest pain and because sometimes there can be serious complications.

The frequency of spontaneous pneumomediastinum is approximately 1 case per 7,000-12,000 hospital admissions.[4, 5] This condition is thought to be more common than previously recognized.[3] Next to pneumothorax, it is the most common cause of chest pain and dyspnea in young patients (15-29 years) admitted to the hospital.[3] Pneumothorax is approximately fifteen times more common than pneumomediastinum.

A recent case of pneumomediastinum stimulated us to review our experience with this unusual entity. Ten cases were identified at either North Carolina Memorial Hospital or the Wake County Medical Center between January 1980 and September 1983.

Table 1 summarizes the clinical findings in ten patients with spontaneous pneumomediastinum. The incidence was 1 case per 12,344 admissions.

The precipitating factors associated with the development of pneumomediastinum were: cough associated with a respiratory illness and/or asthma (six patients), vomiting (2 patients), minor motor vehicle accident (1 patient), possibly associated with weight lifting (1 patient). The diverse precipitating factors associated with pneumomediastinum are given in table 2.[6-11]

Pathophysiology

Macklin and Macklin reported in 1939 the findings of their classic experiments detailing the pathophysiology of pneumomediastinum.[12] Alveoli are of two types: partitional alveoli, whose bases abut other alveoli, and marginal alveoli, whose bases abut vessels, bronchi, connective tissue, septae, or pleura. Pneumomediastinum occurs when the marginal alveoli surrounding a vessel rupture, thereby allowing air to escape into the connective tissue of the perivascular sheath and then to dissect proximally along the vessel to the mediastinum.[3, 12] From there it may escape into the subcutaneous tissues of the neck, chest, face, abdomen or over the entire body. This escape of air into the subcutaneous tissues is important because it lessens the intramediastinal pressure. If air cannot escape, the pressure in the mediastinum can further increase which can impede blood flow in low pressure veins and cause decreased pulmonary artery flow and venous return. Macklin termed this extravascular "air block."[12] Air can also spread into the interstitial spaces of the lung causing "stiff lungs," distally to the pleura causing pneumothorax if the resulting subpleural bleb ruptures, into the pericardium causing pericardial tamponade, and into the abdomen causing pneumoperitoneum or pneumoretroperitoneum.

The alveolus will rupture whenever pressure within the perivascular sheath is negative relative to the intra-alveolar pressure. Partitional alveoli are spared from rupture since increased intra-alveolar pressure can be dissipated among neighboring alveoli via the pores of Kohn. Pneumomediastinum occurs in the presence of atelectasis since the neigh-

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Table 1
Clinical Findings in Patients with Spontaneous Pneumomediastinum

Case	Age (yrs)	Sex	Precipitating Factor	Dyspnea	Chest Pain	Hamman's Sign	Subcutaneous Emphysema (palpable)	Complications
1	18	M	?Weight Lifting ?Spontaneous	+	+	+	−	−
2	17	M	Asthma	+	−	+	+	Small Pneumothorax
3	11	F	Gastroenteritis and Vomiting	−	+	+	−	−
4	15	M	Gastroenteritis and Vomiting	−	−	+	+	−
5	15	M	Asthma	+	−	−	−	−
6	56	M	Motor Vehicle Accident	−	+	−	−	−
7	21	M	Upper Respiratory Illness and Cough	+	+	+	+	−
8	9	F	Upper Respiratory Illness and Cough	+	−	−	+	−
9	2	M	Pneumonia	−	−	−	−	−
10	48	F	Chronic Obstructive Pulmonary Disease	+	+	−	+	−

boring alveoli undergo compensatory over-inflation, thus producing the conditions favoring rupture. Pneumomediastinum also appears when intra-alveolar pressure is greater than that of atmospheric pressure. Pulmonary disease increases the risk of alveolar rupture.[4]

Review of Clinical Findings

The most common chief complaints in our patients were chest pain (5/10 patients) and dyspnea (6/10 patients). The chest pain was located substernally and occasionally radiated to the back or neck. It was frequently aggravated by coughing, swallowing, deep inspiration, and the supine position and was partially relieved by leaning forward. Dyspnea, when present, was usually mild and often related to other precipitating factors such as asthma, upper respiratory illness, etc.

The most common physical findings were Hamman's sign (5/10 patients) and subcutaneous emphysema (5/10 patients). Hamman's sign is a precordial crunching sound and is best heard when the patient is in the left lateral decubitus position.[2, 4] It is synchronous with the heart beat and accentuated by expiration. It is sometimes confused with the friction rub associated with pericarditis. Hamman's sign, though helpful, is not pathognomonic for pneumomediastinum and has been noted in bullous emphysema, pneumothorax, and dilation of the lower esophagus.[4] Subcutaneous emphysema appeared over the extrathoracic trachea and on one or both sides of the neck in five patients. In one patient it extended over the left eyelid, face, neck, and abdomen (Patient 10). One patient in our series suffered a small right pneumothorax which resolved spontaneously without placement of a chest tube.

X-ray Findings

The definitive diagnosis of pneumomediastinum is made by radiologic evidence of free air in the mediastinum. On the posteroanterior chest film, radiolucent streaks of air in the mediastinum, which surround the pericardium, reveal the thin dense line of the anterior mediastinal pleura. The lateral film demonstrates retrosternal free air and clear definition of mediastinal structures such as the aorta. Subcutaneous emphysema in the neck was present on the chest x-ray in all of our patients at the time of presentation.

Differential Diagnoses

Pneumomediastinum must be differentiated from other

Table 2
Causes of Pneumomediastinum

I. Rapid inflations and deflations of the lungs plus increased intra-alveolar pressure.
  Cough
    acute infections
    chronic lung diseases (asthma, sarcoidosis, neoplasm)
  Atelectasis
    pneumomediastinum of newborns
    infections
    foreign body aspiration
  Miscellaneous
    motorcycle riding
    complications of mechanical ventilation
II. Decreased caliber of pulmonary vessel
  Pulmonary embolus
III. Combination of I and II
  Valsalva's maneuver (childbirth, blowing a wind instrument, marijuana, smokers during breath holding)
  Athletes (weight lifting, mountain climbers, heavy breathing after exercise)
  Vomiting (gastroenteritis, diabetic ketoacidosis)
  Submarine escape training, deep sea diving, bomb blast
IV. Trauma
  Perforation of esophagus or tracheobronchial tree
  Chest wounds
  Surgical, dental, or diagnostic procedures

causes of chest pain. Common problems which need to be excluded are: cardiac causes (ischemic heart disease, pericarditis), other pulmonary causes (pulmonary embolus, pneumothorax, pneumonia), musculoskeletal causes (costochondritis, degenerative joint disease) and esophageal causes (spasm, reflux esophagitis, rupture). In two of our patients, chest pain came on after vomiting. In this situation esophageal rupture must be considered. In esophageal rupture the pain is more severe and there is a rapid progression of dyspnea, fever, and signs of vascular collapse. The chest x-ray may show pneumomediastinum, widening of the mediastinum, and frequently pneumothorax and pleural effusion. The diagnosis can be confirmed with an esophagogram. Other causes of chest pain can usually be distinguished by the history, physical examination, chest x-ray, electrocardiogram, and occasionally other laboratory tests. It is important to distinguish air in the pericardial space from air in the mediastinum. In pneumopericardium, the air does not rise above the upper limit of the pericardium on the PA chest x-ray with the patient in the erect position. If decubitus x-rays are taken, pericardial air will shift within the pericardial sac, whereas mediastinal air will not move.[6, 7]

Course and Complications

Pneumomediastinum is usually a benign condition which is rare in adults and more common in neonates.[3, 13] The chest pain is improved within one day and there is resolution of the air on the chest x-ray within 3-5 days. If the free air in the mediastinum accumulates and does not escape into the soft tissues, the pressure in the mediastinum increases. Dissection into the pericardial space can cause tamponade which requires pericardiocentesis.[15] Air can also dissect into the interstitial spaces of the lung causing "stiff lungs" or distally to the pleura where a bleb can form. Pneumothorax results if the bleb ruptures. Unlike pneumothorax, pneumomediastinum usually does not recur.[14]

Treatment

All patients with pneumomediastinum should be thoroughly evaluated by a history, physical exam, and chest x-ray. Particular emphasis should be placed on the recognition of serious complications. Four hours of 95% oxygen decreases the partial pressure of nitrogen in the blood which promotes the diffusion of nitrogen from the interstitium into the blood.[16] This increases the rate of resorption of the mediastinal air. Patients should be given appropriate analgesia and treatment of the underlying disorder predisposing to pneumomediastinum. If complications arise, they should be aggressively treated.

Acknowledgment

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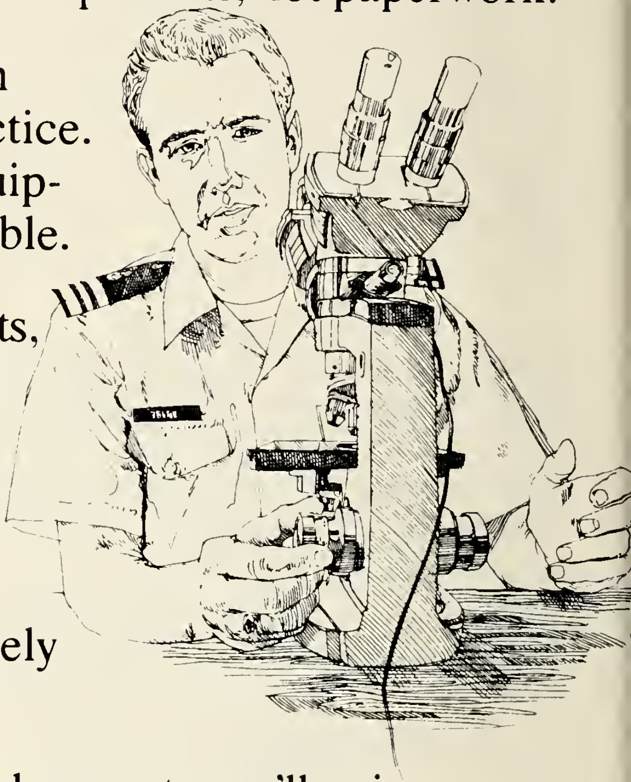

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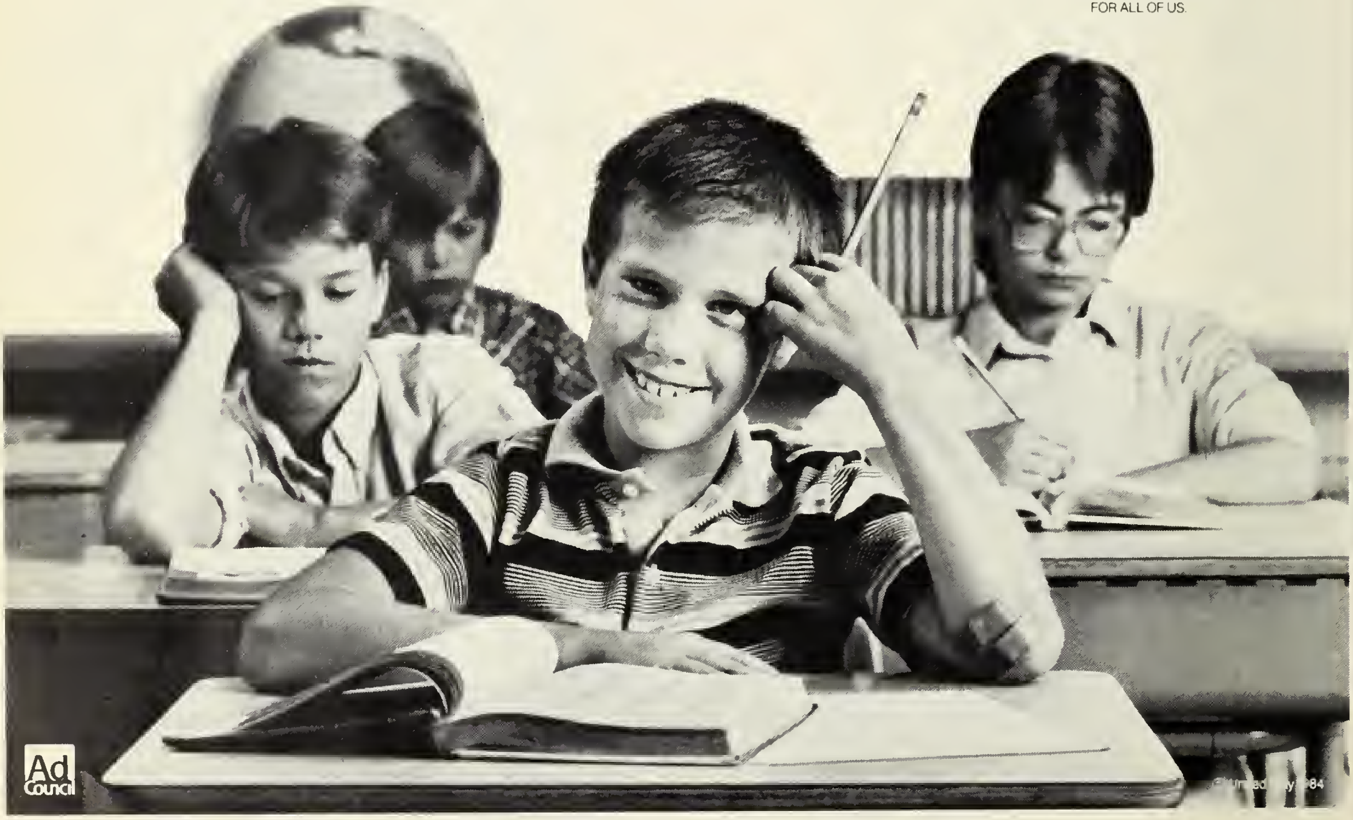

SCIENTIFIC ARTICLE

Interactions Between Digitalis and Antiarrhythmic Drugs

Thomas L. Wenger, M.D. and Harold C. Strauss, M.D., C.M.

• *A review of recent studies of the interactions between digitalis and several antiarrhythmic drugs.*

IN the last several years previously unrecognized actions between digitalis and certain antiarrhythmic drugs have come to light. These interactions can be viewed as having either a pharmacodynamic mechanism or a pharmacokinetic mechanism.

Pharmacodynamic interactions are those in which the response to various drugs is enhanced or diminished by the response to another. Interactions between digitalis and antiarrhythmic drugs include the decrease in automaticity and conduction in the sinus and AV nodes that occurs in combination with beta adrenergic blocking drugs or slow inward current blocking drugs. By separate mechanisms of action, each of these drug types is capable of reducing sinus node automaticity as well as sinus node and AV node conduction so that, when used together, they tend to augment one another's effects. Another well known pharmacodynamic interaction of digitalis with antiarrhythmic drugs involves the use of digitalis in patients with atrial fibrillation to overcome the anticholinergic effects of drugs such as quinidine and disopyramide on ventricular response rate.

Pharmacokinetic interactions are those in which one drug affects how another is absorbed, distributed or eliminated. The interactions of digitalis with certain antiarrhythmic drugs are complex in nature and serve as the focus of this review article. Table 1 gives a list of antiarrhythmic drugs that have been suggested to cause an increase in serum digoxin concentration when both are administered concurrently. Drugs are ranked in decreasing order of their ability to raise the serum digoxin concentration. To understand the potential clinical significance of these interactions, it is important to understand the mechanisms by which they occur.

The first reports of a pharmacokinetic interaction between digitalis and antiarrhythmic drugs focused on the rise in serum digoxin concentration that occurs when it is coadministered with quinidine. This interaction was first described independently by Ejvinsson,[1] Leahey et al, [2] and Doering and Glumel[3] in 1978. Since these initial observations, continuing research has elucidated many questions about this interaction but several important questions still remain unanswered.

The prevalance of the digoxin quinidine interaction appears to be in excess of 90% of patients who are exposed.[4, 5] The magnitude of the increase in serum digoxin concentration has been reported to be quite variable from patient to patient, most studies reporting that at therapeutic concentrations of quinidine a 100 to mean 125% increase in serum digoxin concentration occurs (table 2). While the magnitude of the increase appears to be independent of the serum digoxin concentration, it is clearly dependent on serum quinidine concentration.

When quinidine is given as a loading dose to a patient who is on a steady state digoxin regimen, the serum digoxin concentration rises rapidly. Continued administration of quinidine results in a continued slow increase in digoxin concentration, ultimately reaching a plateau after about 7-14 days. This initial increase is most consistent with an alteration in tissue distribution of digoxin, while the more gradual later rise is consistent with a mechanism that involves a reduction in digoxin's elimination rate.

Any change in tissue binding of a drug causes a change in the apparent volume of distribution. This is defined as the volume that would be occupied by the total amount of the drug in the body if it were uniformly distributed at the concentration found in serum. Thus, the apparent volume of distribution equals the amount of drug in the body divided by the serum concentration. If the amount of drug in the body remains constant, an increased serum digoxin concentration must therefore reflect a decrease in the volume of distribution. This mechanism is considered to be the explanation for the early rise in serum digoxin concentration. A loading dose of quinidine usually results in a 30 to 40% decrease in the apparent volume of distribution. Leahey et al[6] have suggested that there is little effect on the

Table 1
Antiarrhythmic Drugs That Cause Pharmacokinetic Interactions with Digitalis

—Quinidine
—Verapamil
—Amiodarone
—Nifedipine
—Flecainide
—Propafenone

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digoxin volume of distribution when the serum quinidine concentration falls below 1.9 μg/ml.

Elimination of digoxin is dependent on glomerular filtration and renal tubular reabsorption and secretion. In addition, hepatic clearance of digoxin may be important, accounting for as much as 12% of total body clearance. In patients with declining renal function, the reduced renal clearance of digoxin increases the significance of hepatic elimination. It is important to consider all three routes of elimination in evaluating the digoxin quinidine interaction. Available data suggest that quinidine reduces renal clearance by blocking tubular secretion. The range in reduction of renal digoxin clearance is wide but appears to average 30 to 40%. This results primarily from a change in tubular secretion, since creatinine clearance remains unchanged.[7] The influence of quinidine on renal clearance of digoxin can be estimated by subtracting renal clearance from total body clearance or can be approximated by evaluating total digoxin clearance in patients who are functionally anephric.[8, 9] The decrease in non-renal clearance also appears to average between 35 and 45%. This decrease appears to be independent of the serum quinidine concentration.

In summary then, the increase in serum digoxin concentration after quinidine co-administration results from a decrease in digoxin tissue binding, which leads to a decrease in its volume of distribution and a decrease in renal and non-renal elimination.

The tissue compartment from which digoxin is displaced may play a critical role in determining whether the rise in serum digoxin concentration will be associated with an increase in digoxin effect and toxicity. For example, if the displacement occurs only from non-specific binding sites in the body, then an increase in serum digoxin concentration will likely cause an increase in the action of digoxin. If, on the other hand, displacement occurs at the receptor site responsible for its actions, such as sodium, potassium (Na^+, K^+) ATPase, then the increase in serum digoxin concentration may not be accompanied by an increase in effect or toxicity and, in fact, could be associated with a decrease in digoxin action. This important area of basic research remains unsettled and is critical to an understanding of the expected clinical effects of the interaction.

An effort to elucidate the clinical significance of the digoxin-quinidine interaction has centered on efforts to demonstrate the clinical effects of the increase in serum digoxin concentration. Indices that have been used to evaluate the effect of a rise in serum digoxin concentration on function are assessments of the PR interval as a reflection of vagomimetic effects and of systolic time intervals reflecting the direct effects of glycosides on contractility. Such studies are complicated since both quinidine and digoxin are capable of having multiple effects on electrocardiographic and systolic time intervals. Leahey et al[10] examined the change in serum digoxin concentration during administration of four antiarrhythmic agents: quinidine, procainamide, disopyramide and mexiletine. Only quinidine caused a significant increase in serum digoxin concentration (figure 1). When the effects of these four agents on the PR interval were examined, only quinidine caused an increase in the PR interval even though each of these antiarrhythmic drugs tends to have a similar effect on the AV node (figure 2). One might surmise, therefore, that the increase in PR interval was secondary to the rise in serum digoxin concentration rather than the co-administration of quinidine.

The effect of co-administration of quinidine on contractility has been assessed by systolic time intervals.[11] Though the data support the view that the increase in serum digoxin concentration results in an increase in cardiac effect, the study does not really address how large is the increase in cardiac effect resulting from the increase in serum digoxin concentration.

Ultimately, the significance of this interaction needs to be defined by clinical observation as well as by basic and clinical research. Several case reports have cited experience in which digoxin toxicity developed following quinidine administration despite a constant digoxin dose, stable renal function and a normal potassium level. On the other hand, Walker et al, reporting on the observations of the Boston Collaborative Drug Surveillance Program, noted a rate of 1.1 reactions per 100 patient days in 4,027 patients who received digoxin alone, 1.1 reactions per 100 patient days in 249 patients who received quinidine alone, 2.9 reactions per 100 patient days of observations in 142 patients who received digoxin and quinidine. The difference in reaction rates in patients receiving both drugs and the sum of the rates in patients receiving the drugs separately were not significantly different.

Any analysis of the clinical impact of co-administration

Table 2
Effect of Quinidine on Serum Digoxin Concentration

		Serum Digoxin Concentration			
	n	Quinidine Concentration	Digoxin	Digoxin + Quinidine	% change
Leahey et al 1978	27		1.4±0.7	3.1±1.4μg/ml	121
Ejvinsson 1978		2.1μg/ml	0.85	1.6μg/ml	88
Doering 1979	38	2.32μg/ml	0.98±0.37	2.47±0.64μg/ml	152
Mungall et al 1980	15	2.82μg/ml	0.72±0.28	1.41±0.43μg/ml	96
Leahey et al 1980	22	2.7μg/ml	1.2±0.8	2.4nmol/1	100

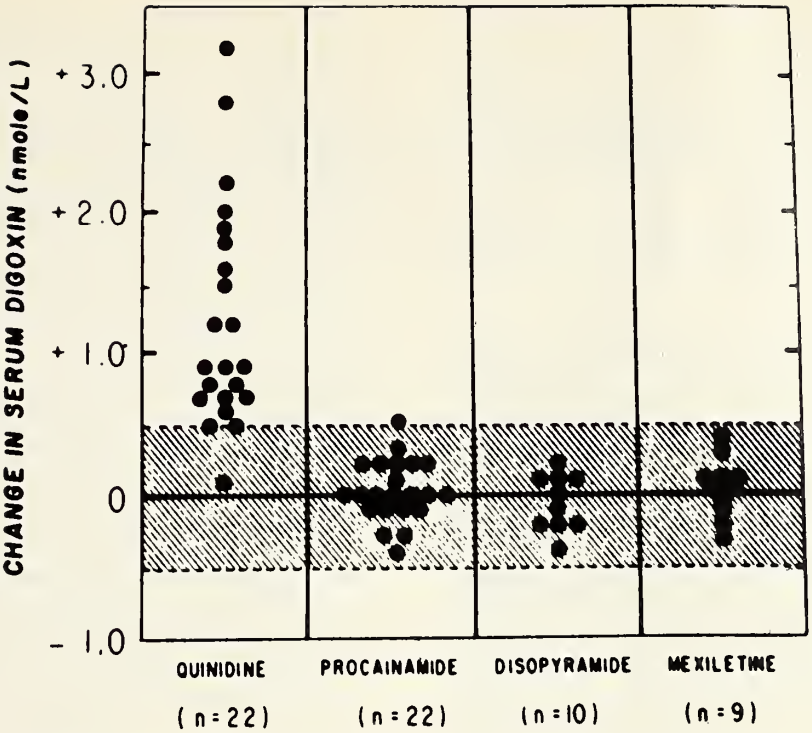

Figure 1. *Each point represents the difference between serum digoxin concentration before and after administration of the antiarrhythmic drug.*

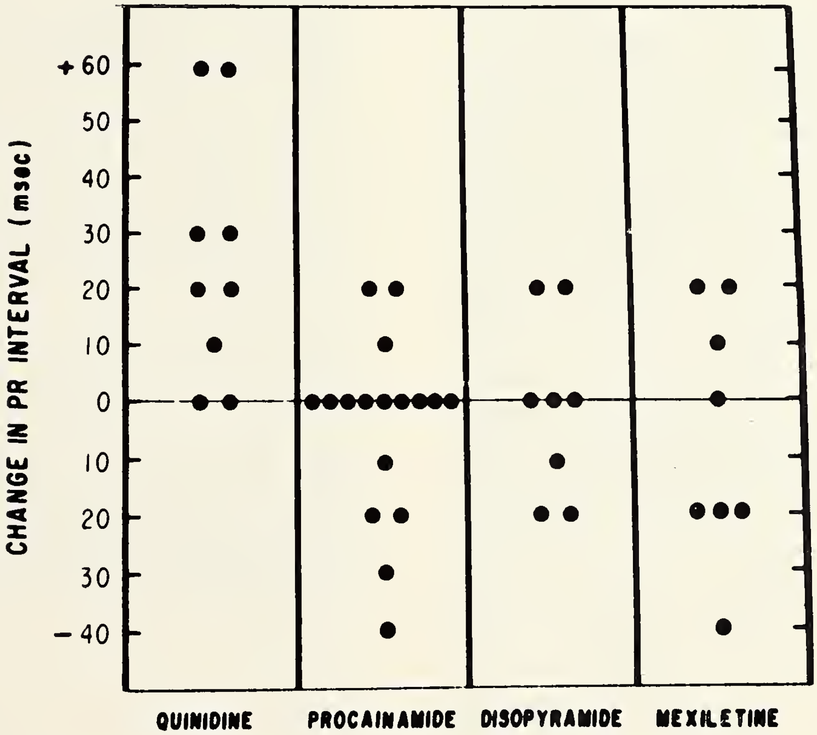

Figure 2. *Each point represents the difference in PR interval before and after administration of the antiarrhythmic drug.*

of digoxin and quinidine on digoxin toxicity will depend on the serum digoxin concentration prior to quinidine exposure, the serum quinidine concentration and the toxic threshold for digoxin in that particular patient or patient population. Clearly, patients whose serum digoxin concentration is at the upper level of the therapeutic spectrum will likely have a higher prevalence of toxicity than those with serum digoxin level concentrations at the lower level of the therapeutic spectrum. Such confounding variables make definitive conclusions from the clinical data difficult to achieve.

Although this paper has concentrated on the digoxin quinidine interaction, data also exist on a digitoxin quinidine interaction. Although initial reports suggested that such an interaction did not exist, Fenster et al[13] showed that the interaction appeared to reach the same magnitude as the digoxin quinidine interaction if assessments were made far enough out in time. The different time course relates to the much longer half-life of digitoxin. Although there appears to be little change in the apparent volume of distribution of digitoxin, elimination is prolonged. Because of the prolonged elimination half-life of digitoxin, the time taken to reach a new steady state may be in excess of one month. It is thus unclear whether digitoxin can be considered an alternative to digoxin when considering quinidine therapy in a patient requiring a digitalis glycoside.

Besides quinidine, other antiarrhythmic drugs have been shown to have effects on digoxin kinetics. Data by different investigators suggest that verapamil causes a 60 to 75% increase in serum digoxin concentration via reduction in both renal and non-renal clearance and perhaps also by reduction in the volume of distribution of digoxin. Pedersen et al[14] found that this digoxin verapamil interaction was dose dependent and partially reversible with continued therapy.

Amiodarone, an experimental antiarrhythmic drug, appears to produce a significant increase in serum digoxin concentration if the amiodarone is given in large enough doses. A recent study indicates that an increase in serum digoxin concentration may be particularly marked in children, ranging between a 69 and 278% increase in the serum digoxin concentration in a prospective study and up to 800% in a retrospective study.[15] The authors of this investigation suggested that the interaction might be more significant in children because of a greater rate of renal tubular excretion of digoxin in children.

Initial reports suggesting a 45% increase in serum digoxin concentration during co-administration of nifedipine and digoxin have not been confirmed in subsequent studies. Small and as yet unsubstantiated claims for an increase in serum digoxin concentration have also been reported for flecainide and propafenone. The existence of such interactions, the magnitude of the effect and the clinical significance remain to be elucidated.

What practical suggestions can be offered to the clinician caring for a patient who requires digitalis therapy and antiarrhythmic drug therapy? The first practical suggestion is obviously to reassess the need for digitalis or for the antiarrhythmic drug. If both forms of therapy are considered essential it is probably still prudent to follow the guidelines elucidated by Dr. Bigger in 1981.[16] He suggested that the dose of digoxin be decreased when quinidine is added. If a loading dose of quinidine is given, then the digoxin dose for that day can be omitted and, if quinidine is continued, the digoxin maintenance dose should be decreased by about one half. It may be useful to follow serum digoxin concentrations since the magnitude of the interaction can be variable. In any case, careful clinical evaluation of the patient for a period of time equivalent to at least five times the elimination half-life of digoxin after addition of the quinidine is essential. An alternative approach is to replace quinidine with another antiarrhythmic drug, such as procainamide or disopyramide, that does not affect the serum digoxin concentration. Guidelines for coadministration of digitalis and verapamil and amiodarone are even less clear. Although it would be prudent to follow the serum digoxin concentration as a guide to readjusting the digoxin dose, clinical evaluation of the patient remains of paramount importance.

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SPECIAL ARTICLE

Thoughts on the Beliefs of Religious and Medical Institutions

Albert D. Warshauer, M.D.

- *One physician's look at some of the most difficult issues facing the world near the end of the twentieth century.*

Introduction

We begin with definitions.

"Education" is the acquisition of a system of beliefs and skills.

An "institution" is a group of different people, who by being partially restrained to one another, acquire one or more significant new properties not found by testing the individual people. Thus, to prove that an institution exists, we must show first, a partial restraint between different people, and second, a significant new property.

An institution which itself largely controls the entry and exit of its members is "self-perpetuating."

Is medicine a self-perpetuating institution? Yes. People must pass tests to be allowed to practice medicine; and their work, at least in hospitals, is subject to staff review. New properties are that physicians can prevent or ameliorate many diseases better than can lay people. Physicians largely control the education and tests of people who wish to become and remain physicians. By their common education, physicians acquire a system of beliefs.

Religions likewise often are educating, self-perpetuating institutions. The partial restraint is the religion's criteria for membership. New properties include a special system of beliefs and social meetings of the members of the group. (A person could have a unique system of beliefs and live as a hermit, but such people are few compared to the members of organized religions.)

Can the membership of medical and religious institutions overlap? Yes, of course. Some physicians belong to religions; others do not. Some members of religions are physicians, whereas others are not.

The beliefs of an institution can be a source of problems. Sometimes the beliefs of one institution are contrary to the interests of another institution or opposed to the welfare of the whole society. Sometimes the beliefs contradict one or more natural laws, or the beliefs have an unusual historical origin. Beliefs considered to be true without regard to tests are said to be "Sacred."

"Bias" is a certainty of belief without supporting tests or evidence. "Prejudice" is bias favoring one's own advantage and to the disadvantage of someone else. Bias which operates to one's own disadvantage is "reverse prejudice."

From the viewpoint of a scientist who does not belong to a religious or medical institution, Sacred beliefs tend to bias the person who holds them. But a member of the religious or medical institution which holds Sacred beliefs often considers these beliefs to be irrefutably true, and therefore to be neither bias nor in need of testing.

Underlying Theorems

Several scientific theorems apply to religious and medical institutions and to their interactions.

1. People and institutions sometimes want more rights (freedoms) and less duties (responsibilities).

Explanation: Freedoms often can aid our satisfaction of needs and desires, while duties can inhibit our efforts. In other words, more freedoms and fewer duties sometimes promote survival and growth.

2. Institutions and societies often seek stability.

Explanation: Some stability is necessary for the formation, maintenance, and growth of institutions and societies.

3. Need for feedback from actions.

For social stability, the people in control must be accountable to the people who are affected by their decisions. Rights and responsibility must coincide to a reasonable degree. Otherwise, instability and social conflict sooner or later become inevitable.

4. Limited rights.

Rights are not total. Our freedoms extend only to where they infringe on the rights of others. This limitation applies to freedoms of speech, press, and systems of beliefs.

5. On existence of bias.

Sometimes, the resolution of a problem affects the welfare of the participants. That is, the people and their institutions may gain or lose privileges and money by what actions are taken.

Whenever an institution has a self-interest in how a problem is resolved, we can suspect the existence of bias by the institution and its members. Religious and medical institutions share this propensity to be biased.

6. On visibility of bias.

Ordinarily, neither people nor their institutions are aware of their own bias.

A person's own bias may be obvious to outsiders, but it is transparent to himself. It has been said that prejudice is the

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only thing which cannot recognize itself in a mirror.[1] (Personally, I have almost no bias or prejudice, and cannot understand why people laugh when I say this!) Usually more heat than light is generated by accusing someone of bias.

7. On the difficulty of changing bias.

Bias is not hardened steel — but occasionally it does seem to be cast in concrete.

Bias sometimes can be changed by presenting facts which contradict the bias, and by asking the person to explain how the facts can mesh with his bias.

Or, if the subject holds inconsistent beliefs, you can ask how this happened. Did he acquire one of the inconsistent beliefs first, or both together? Did he first learn (a) that all members of religion X were Communists, or (b) that all of them were rich Capitalists?

We should not be very optimistic regarding changing a person's bias. If a person could easily realize that he was biased, he probably would not have become biased in the first place.

Therefore, in resolving problems between different institutions or between an institution and the whole society, we usually should seek social stability and limit the infringement of rights, and only secondarily try to influence the belief systems of the protagonists.

Origin of Problems Due to Different Beliefs

The belief system of one institution may or may not agree with that of a second institution or with the whole society. When the parties agree, their interactions will likely be easy and without problems. Religious and medical institutions often are supportive and helpful to each other.

However, when the institutions have competing beliefs on a subject of mutual interest, friction becomes likely. If one or both institutions regard their beliefs as "Sacred," resolution of the problem becomes difficult.

Illustrations

Let us examine actual cases and possible resolutions.

1. Suppose the religion refuses medical care

A member of a religious sect may refuse medical care for himself or for dependent members of his family. Since the member is responsible, he should be permitted control. The physician has no inherent right to object unless the physician is willing to assume responsibility for the outcome.[2]

Suppose the physician objects to not operating on a newborn baby who has spina bifida and lower extremity paralysis.

If the medical institution and society require the operation over the parent's objections, they should offer to raise the baby. Otherwise, they seek rights without responsibility. Physicians who insist on operating on such patients, fully knowing that they are imposing an unwanted, serious burden on the family, are irresponsible.

What about the baby's rights? Since a baby cannot voice his opinions, someone must speak for him. It would seem that the parents, who gave birth to the baby and are responsible for his prolonged care, have more right to represent the baby than the physician who only recently became involved and is not responsible for the later daily care of the baby.

It is arrogance on the part of the physician to assume that his superior knowledge gives him a right to impose unwanted burdens on families. Here, the physician's job is to advise, not to decide. If the physician truly has superior knowledge, let him employ it for persuasion, and not for coercion of the responsible parties.[3]

2. On birth-control, sterilization, and abortion

Suppose an institution, such as a religion, wants to outlaw contraception, sterilization, and abortions. Then the members of this institution should assume responsibility for the resulting offspring. If they personally avoid this responsibility, their intentions become suspect.

If a pregnant patient wants an abortion, she is within her right, since she and no one else is responsible for the baby continuing to live.

If people want the right to prevent this abortion, then they should accept responsibility — which could mean raising and feeding the child. Otherwise, their actions are a cheap effort to obtain a right without a corresponding duty.

3. On suicide and euthanasia

Suppose a patient, who is terminally ill with cancer or another incurable illness, wants to commit suicide. Society has no forcible right to prevent this suicide since it has no way to improve the patient's lot.

If the ending of life requires an initiative, such as injection of a drug, the physician is fully within his rights to refuse. However, if the termination simply requires that extraordinary measures such as ventilators and dialysis machines be discontinued, we should accede to the patient and family's request.[4]

To actively kill is one thing; to actively prolong misery is quite a different matter.

4. Blood transfusion

A religious sect allows its members to receive only their own blood. For elective procedures, many surgeons collect blood from these patients preoperatively. If blood is needed, the patient's own blood is used.

However, suppose a patient in need of major surgery has religious beliefs which prohibit his receiving a blood transfusion from other donors and the patient cannot supply his own blood units.

The physician has a choice. He can either treat the patient and respect his religious beliefs, or he can refuse to care for the patient. But the physician should clarify to the patient exactly what he thinks are the options as well as the contingencies in the event of a mishap.

For example, an anesthetist might say, "I will do everything possible to avoid giving you a blood transfusion. However, if something unexpected happens which places you in critical danger, I will administer a transfusion. It is against my religious beliefs to allow patients to die during an operation from not receiving a needed transfusion. I respect your religious beliefs, and hope that you also can understand mine."

If the patient wants me to promise not to transfuse him, I might say, "I will gladly do so, providing you will promise that you will not be in urgent need of a transfusion."

The problem is resolved by realizing that one person's rights stop where they start infringing upon another person's rights. Religious beliefs should not be an excuse for what, under other circumstances, would be clear and obvious malpractice.

5. *Autopsy*

Suppose a religious group wants to prevent autopsies. If the cadavers during life were their relatives, the religious group has legal control. Otherwise, if not related, the religious group wants to interfere with medical education without accepting responsibility.

6. *Special diets*

Suppose patients want, or contrarily do not want, some special foods. Such diets usually are a minor inconvenience, and can be catered without serious problems.

7. *Allergy as a cause of bronchial asthma*

It is not only patients who are affected by bias. Physicians also have been taught religious and medical beliefs.

A basic tenet of allergy is that different species of animals respond notably differently to antigen-antibody reactions.

Physicians who in their youth were biased in favor of the separate creation of species will tend to favor this tenet. They want the animal species to be different, and will tend to avoid critical tests of this hypothesis.

Contrarily, physicians who favor evolution will be suspicious of this tenet.

For example, bronchial asthma in children is sometimes attributed to allergy to food, such as cow's milk. No experimental animal has been found to develop bronchial asthma from drinking cow's milk. Cats drink milk, but have you ever seen a cat which routinely developed asthma after drinking milk? I have not. Nevertheless, this hypothesis of allergy was thought to be a reasonable etiology of bronchial asthma in children.

8. *The right of physicians to decide on medical care*

Because of our superior medical knowledge, we often assume that we have a right to decide on the care of patients. In fact, our decisions usually do benefit everyone concerned. However, whenever a right is divorced from responsibility, a prospect exists for abuse.

Part of the current belief system of physicians seems to be that life should be prolonged or saved. Ordinarily, this belief is an excellent goal. However, sometimes the quality of the extended life seems to be less important than its prolongation.

Suppose a patient has a severe chronic brain syndrome and is vegetating in a nursing home. No visitors come to see the patient. A leg becomes gangrenous. The surgeon decides that an amputation should be done, and I anesthetize the patient. The surgeon and I receive a fee, but society pays the bill. The patient vegetates a few months longer and dies.

Society at large, not the surgeon and myself, has been taken advantage of because physicians have received a right without a corresponding responsibility.

A common way of running up a large medical bill is to place a patient on a ventilator and intravenous feeding during the final few hours or days of a terminal illness. These large bills may help keep hospitals financially solvent; but, for the entire society, this kind of medical care is a waste of resources.

9. *On medical fees and malpractice awards*

Physicians like to receive high medical fees and not to be subject to high malpractice awards. The general public favors the opposite, low medical fees and high malpractice awards. The malpractice lawyers who work on a contingency basis, of course, want no cap on malpractice awards.

Both the physicians and the public apparently want maximal rights without matching responsibility. Neither side will admit that fees and malpractice awards are linked problems. As a result, the public fears medical fees and physicians fear malpractice suits.

It seems doubtful that this problem will be resolved until this link between medical fees and malpractice awards is acknowledged by both sides.

10. *Indifference to large social needs*

The belief system of physicians often emphasizes individual patients. Taking care of individual patients brings substantial financial rewards. But little monetary gain accrues to physicians from attending to large social needs.

Let us examine the record. We occasionally have done very well in answering social needs. Physicians in cooperation with other organizations accomplished widespread polio immunizations. Poliomyelitis has become a rare disease in the United States.

But in a few areas, our record is dismal.

- Many physicians were passive during the Vietnam war. Few took a public stand, one way or the other.
- Physicians also were largely inactive during the civil rights struggles a few decades back.
- Nor, as a group, did we distinguish ourselves in promoting the use of seat-belts and in opposing drunk driving.

However, we do wake up promptly when our economic interests are affected. When dentists apply for operating privileges in hospitals, we become alert.

When laymen regard the American Medical Association as a union, they have more than trivial grounds for their opinion. Physician organizations have been politically active in aiding candidates who favor our economic interests. But what have we done in favoring candidates who will take a stand on controlling overpopulation and slowing or stopping the nuclear arms race? Not much.

Human overpopulation and the nuclear arms race are two underlying problems in the world.[5, 6] Related problems include religious bigotry, terrorism, our lack of a reliable means for settling international disputes without wars, and the loss of valuable plant and animal species. In the United States alone, our present rate of depletion of natural resources should be alarming to a thoughtful observer.[7]

Physicians put in an artificial heart and keep one patient alive a few extra weeks. At the same time, we ignore that more than 10,000 children are being born who are fated to starve before they are six years old. I find nothing wrong with heart research, and strongly support it. However, I wonder about our system of medical beliefs which so largely ignores the overpopulation in the United States and the rest of the world.

11. *On international cooperation and conflict*

The indifference of physicians concerning international issues is striking. It is a rare event when a physician writes a letter to the editor or publicly takes a stand against terrorism.

In World War II, more than a million children of religion

X were murdered. Some children were bled to death by the Nazis to provide blood for transfusions of soldiers. Some Nazi physicians killed people by experiments involving hypoxia and by submersion in ice water. Was there a public outrage by physicians? I saw little concern, a few letters and articles regretting this unpleasant chapter of history. The Holocaust did not upset many physicians of religions Y and Z, perhaps because the victims belonged to a different religion X. So far as I can see, physicians have about the same religious bias as the remainder of the population.

12. On the future of medical practice

Our current medical belief system holds that medical care is best provided by physicians and medical institutions engaged in private practice. This method of medical care furnishes strong incentives to physicians and rewards those who are skillful and work hard.

In a wealthy society, the private practice of medicine can flourish. Medicine has made tremendous advances in the United States.

However, as the United States becomes progressively more overpopulated, our average wealth shrinks. In a poor society, the private practice of medicine can become a destabilizing influence. If the leaders of society find that the private practice of medicine is no longer affordable, it can be replaced by some other kind of medical practice.

I have heard a few young physicians say: "Socialized medicine is inevitable. So we should make some money while we can." With this attitude, accompanied by an indifference to the major problems facing our people, such predictions could well come to pass.

At present, the problem of human overpopulation seems to be getting worse. The related problems of the nuclear arms race, religious bigotry, and terrorism do not seem to be getting much better. Perhaps we should re-examine the belief systems of our religious and medical institutions.

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North Carolina Medical Journal

Features for Patients January 1985

Home Care, An Alternative to Institutionalization:

Nurses in Action

Laura Lacy

At some time in our life, many of us may be forced to reach a decision regarding institutionalization versus home health care, for as we age so do our parents and grandparents.

Unfortunately, the majority of us have been unschooled in the pro's and con's of each option.

Until the mid-1960s, institutionalization, regardless of appropriateness, was the accepted standard of health care delivery in the United States. Construction of facilities boomed, and with these beds available, nursing homes, convalescent centers, and retirement facilities sprang up everywhere.

At the first sign of illness or aging, in came the movers, out went the accumulated memorabilia of a lifetime and into a home went Mom. It did not seem to matter whether she liked it or not or even if she really belonged there. She was safe, well taken care of, and it was thought she would be able to live out her remaining years in comfort and security.

The revolt toward deinstitutionalization began when people started looking at the costs associated with this "confinement policy." Many began to listen to the home health care advocates' arguments on the social impact this situation was having and saw the morbidity statistics: the average patient confined to a nursing home lived in that environment a scant 19 months. Why? Was it because they had entered so very ill or, as many health care professionals believe, was it that their quality of life had changed so drastically that they no longer cared about living?

In light of these considerations, home care offered an attractive alternative to institutionalization. While in many instances the institution is the ideal situation, home care is and should be the ideal situation in others.

A home care program can mean many different things. As each patient has a differing need, the home care program must be developed to satisfy the individual's requirements. In many cases, companionship, meal preparation, and housekeeping services are the primary requirements.

The simplest definition of home health care is the provision of health care related services to persons in their place of residence. A home health care program can encompass many types of care. An evaluation of the person should be conducted which takes into account the diagnosis and prognosis, the patient's physical and social needs, diet, and therapy. The nursing implication should be assessed and determined and the availability of resources explored.

A comprehensive individualized nursing plan then should be tailored to meet the patient's requirements as indicated by the physician's plan of treatment. This care plan should detail the type(s) of service(s) to be provided, any equipment and supplies that may be required, and the level of personnel needed to perform the tasks. This could mean an R.N., L.P.N., home health aide, or physical therapist. A successful home care program must have one inherent component: it must be flexible and adjustable to satisfy the individual's changing needs.

While considerable attention has been directed at home health services for the elderly, a home care program can be tailored for anyone requiring direct or supportive assistance. A particular concern also may be the handicapped or developmentally impaired child who survives his parents, orphaned minor children, or a patient of any age who has a temporary or permanent physical ailment or limitation.

In most locations in North Carolina, there will be one or more home care providers available to carry out all these services. They are listed in the yellow pages of the telephone book. These offices are staffed by profes-

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sionals knowledgeable about Medicare, Medicaid and private insurance coverage who can inform the consumer of these facts.

In the United States, Americans are still struggling to discover the best way to care for dependent persons. The acceptance of the "new" home care movement appears to be dawning. William Buckley, author and columnist, is quoted as saying, "It has been widely acknowledged — though there are those who recognized the point — that the principal problem socially in America during the next 20 or 30 years is not going to be the problem of overpopulation, nor Soviet recklessness, nor nuclear war, but the problems of caring for the aged." In the past 20 years, we have increased by 10 years the predictable actuarial lifespan of the man who is 65 years old. As a result of heroic geriatric efforts, we have prolonged the efforts of our parents and grandparents to a point that is a tribute to our instincts to permit people to live as long as they can. But as so often happens, it is an instinct that does not face some of the complementary problems that go with it — the necessity of expanding home health care services.

There are times when it is appropriate for a person to be placed in a nursing home and other times when this placement is ill-advised. As no one wishes to see anyone prematurely institutionalized, responsible home care professionals do not advocate unrealistic home care programs. In the absence of a public long-term care policy, home health care providers have become committed to a community-based, in-home support service.

Consumers also have become committed to caring for their relatives (or themselves) within the home environment. The 1980s will see an even greater demand placed on nursing services for trained home care personnel. The size of our senior citizen population is rapidly growing; the costs associated with long-term confinement are skyrocketing while our nuclear family is shrinking; and previously full-time homemakers are entering the work place in droves. Home care remains a psychologically advantageous and cost-effective health care modality. Patients thrive and families benefit from a professionally developed, appropriately tailored health care program, relieving the burden faced by many families.

Helen Hayes, the noted actress and an outspoken advocate of home health care, recently appeared before the Senate Labor and Human Resources Committee to request federal aid for home care. The 81-year-old actress is quoted as saying, "The changes demanded by old age are tough to accept. Maintaining as much independence as you can makes it easier to yield gracefully to lengthened life. Now we must learn to make a longer life worth living. Older people deserve choices all over America, and we realize what we might have known from the start: for most of us, there really is no place like home."

The editor recently attended a conference on geriatric care sponsored by the Veterans Administration. Some 10 groups offering home health care services were invited to attend. Mrs. Lacy was the only one to respond. She contributed to the conference, and for this receives some free advertising in this issue of the *Journal*.

EAS

PRURITIS ANI

Claude S. Burton, M.D., Russell W. Eyre, M.D., and J. Lamar Callaway, M.D.

While it may be true that it is "better than riches to scratch where it itches," in the case of pruritis ani, or perirectal pruritis, such indulgence may be embarrassing. A careful observer of any large crowd will note that many among us suffer with rectal itching. Since not even television has ventured into this taboo but common public health problem, it is appropriate to do so in the medical journals. We hope our comments will be useful to many silent sufferers.

Pruritis ani is ordinarily a simple problem with a relatively simple solution. Though an occasional patient will have an infection (due to bacteria, yeast, or fungi), skin cancer, or coincidental involvement of another skin condition such as psoriasis or seborrheic dermatitis, the vast majority of cases relate to physical/mechanical difficulties in the area. Invariably, there is some element of fecal soilage. Fecal contents are highly irritating to the sensitive skin around the anus. Even a small amount of fecal material when rubbed between the cheeks throughout a day of walking, sitting, and bike riding will produce irritation and itching of the surrounding skin. A brief walk on all fours suggests that this frictional problem is one of the consequences of our upright posture.

Fecal soilage has many causes. Loss of muscle strength in the perianal musculature will reduce the natural function of the anal sphincter or valve. Under pressure or gravity, inevitable fecal soilage occurs to the perianal skin. Trauma (childbirth, anal intercourse), neuromuscular disease (strokes, diabetic nerve damage), and mechanical problems often related to the presence of hemorrhoids, will interfere with function of this valve and lead to rectal leakage. Commonly, closely spaced hips and hair, especially in men, prevent adequate cleansing following defecation. The "single tissue" dispensers found in many public restrooms surely contribute to the problem.

In evaluating patients seen in our clinics with pruritis ani we routinely explore the regional anatomy to rule out mechanical and neuromuscular problems. Hemorrhoids may or may not require surgical therapy depending on the individual situation. Conservative care will usually suffice. A careful search for infection with bacteria, yeast, or fungi is routinely performed. At the same time we search for evidence of other skin diseases such as psoriasis. In many cases we ask the patients to obtain scotch tape preparations of perianal skin early in the morning to examine for the presence of pinworms. A history is taken to rule out the possibility of allergic contact dermatitis due to various topically applied medications, perfumes, etc.

The diet, which influences bowel function and stool composition for obvious reasons, is often a contributing factor. Stimulants contained in many soft drinks, coffee, tea and chocolate may have undesirable effects in patients with pruritis ani. Hot, spicy foods are occasionally implicated. Curiously, some foods which produce no allergic reaction in the bowel, such as cashew nuts, are relatives of the poison ivy plant and may produce a dermatitis when they reach the perianal skin.

The most important aspect of treatment is to keep the skin of the anal area clean and dry. In cases where extensive abrasion has occurred, prevention of further friction, rubbing and excessive wiping are mandatory. Many topical medications will only worsen the problem of moisture and irritation. Soaps are notorious for accumulating in this area and are highly irritating. We recommend that patients use water alone to clean the area when they shower. After bowel movements it is critical to remove all fecal contents. Wet cotton or tissue is better than dry toilet paper for this purpose and we find pre-moistened wipes such as Baby Fresh by Scott Paper Company a useful alternative. These may be carried in a baggie for use on the go. After thoroughly cleansing the area it is important to pat the area dry without rubbing. If you are the sort who notes leakage on your underwear then we suggest you wear a thin, cotton pledget applied directly to the anus between bowel movements. This should be small enough so that you are not aware of its presence. Consider thoughtfully your bowel habits. If you are the sort who ignores the call to nature until it is convenient, then you are undoubtedly contributing to the problem. If constipation is a problem, it should be addressed. An increase in fiber in the diet such as a bowl of Raisin Bran each morning is often all that is required.

The intensity of treatment varies directly with the severity of the problem. In some cases, topical steroid lotions are necessary to break the itch-scratch cycle. In others, a Prednisone taper may be necessary, particularly if topical therapy is irritating. In all cases, medication is part of an overall plan and not a substitute for the measures described above.

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SOCIOECONOMIC ISSUES

The Top-Heavy Plan Rules: What Will They Do to Your Retirement Plan?

Walter R. Rogers, Jr. and Jennifer M. Dibble

- *A continuation of the retirement plan advice for physicians begun in the October 1984 NCMJ.*

I. Introduction

IN our last article we introduced the phrase "top-heavy plan" and promised to define it later. This article will discuss what "top-heavy" means and what effect being "top-heavy" may have on your present or contemplated qualified retirement plan.

Before the Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA), tax law imposed stricter rules on retirement plans of unincorporated practices than on those of incorporated practices. Recognizing that this disparity in qualified retirement plans caused many professionals to incorporate their practices purely for tax reasons, Congress decided to equalize corporate and non-corporate retirement plans in most respects. TEFRA lifted some of the limits on non-corporate plans, primarily the lower contribution limits. However, TEFRA also extended many of the limits on non-corporate plans to all plans that provide greater benefits to certain, usually higher paid, groups of employees. These limits, along with others introduced by TEFRA, are the top-heavy plan rules. Thus, whether or not you have incorporated your practice, you must consider and respond to the top-heavy plan rules. In addition, whether or not your plan actually is a top-heavy plan, your plan documents must contain top-heavy plan language, which comes into effect if your plan becomes top heavy.

II. Definitions

As with most tax matters, the key to understanding the top-heavy plan rules is understanding certain terms that appear in the tax law.

A. *"Top-Heavy Plan"*

Almost any plan, whether a defined contribution plan such as a money purchase plan, or a defined benefit plan, can be a "top-heavy plan." A defined contribution plan is top heavy if the total of the accounts of key employees is more than 60% of the total of the accounts of all employees under the plan. A defined benefit plan is top heavy if the total value of accrued benefits of all key employees is more than 60% of the total value of accrued benefits of all employees under the plan. Certain plans of the employer are tested in the aggregate for purposes of the top-heavy determination. The definition of a top-heavy plan quickly leads to more questions. When is the top-heavy determination made? What is included in an account or in the definition of accrued benefit? Who is a key employee?

B. *"Determination Date"*

Each year an employer must determine on the "determination date" if its plan is top-heavy. The determination date is generally the last day of the preceding plan year or, in the case of the first plan year, the last day of the first plan year. The value of accounts and accrued benefits as of the determination date is the value determined on the most recent valuation date within the previous twelve months. The valuation date must be the same as the valuation date used for computing plan costs for minimum funding. Most plans will have the same valuation and determination dates.

A plan can theoretically change from top-heavy to non-top-heavy and back again as often as once a year. However, most physicians' plans are top-heavy, and are likely to remain so.

C. *Accounts and Accrued Benefits*

An employee's account in a defined contribution plan consists of all employer contributions made or due to be made on the employee's behalf to the plan as of the determination date, any income or gain on those contributions, and the employee's share of amounts forfeited by other employees leaving service before complete vesting. Accrued benefits in a defined benefit plan consist of the present value of benefits which would be paid to the employee upon retirement if the employee terminated employment on the date the accrued benefits are valued.

There are two additional categories of funds included in an account or in accrued benefits. First, all distributions to employees made within the last five plan years are added back into the account or accrued benefit. Second, all after-tax employee contributions, whether voluntary or required to be made under the terms of the plan, are included. Voluntary deductible employee contributions and certain rollovers from one plan to another are not included.

From the law firm of Smith, Anderson, Blount, Dorsett, Mitchell & Jernigan, Box 12807, Raleigh 27605.

D. "Key Employees"

Congress devised the phrase, "key employee," in an attempt to include all persons who exercise some amount of control over an organization and presumably its retirement plan. Key employees are employees who are or were within the four preceding plan years, certain officers, a shareholder or partner owning a certain percentage of the employer, or one of the ten individuals owning the largest interests in the employer and earning more than $30,000 per year. (For plan years beginning after December 31, 1983, officers will not be key employees merely because of their status as officers unless they also have an annual compensation from the employer of more than $45,000.)

Most physicians will be key employees for purposes of their retirement plans. If the practice is incorporated, the physician may be a key employee because of being an officer earning more than $45,000. He may be a key employee because he owns more than 5% of all the stock or 5% of the stock voting power of the practice. He will also be a key employee if he owns more than 1% of the stock or stock voting power and receives more than $150,000 in annual compensation from the practice. If the practice is not incorporated, the physician owning more than 5% of the capital or profits interest of the practice, or more than 1% with more than $150,000 in annual compensation, is a key employee. A final catch-all category includes any of the ten employees who own the largest interests in the employer and earn more than $30,000 per year. The physician could be a key employee in more than one category but his account or accrued benefits will be counted only once each year in applying the top-heavy test.

There are two further refinements. First, certain "attribution rules" apply so that if, for example, a husband and wife practicing together each own 3% of the stock of the practice, each physician's stock ownership will be attributed to the other and both will be key employees owning more than 5% of the stock. Second, the beneficiary of a key employee is counted as a key employee. For example, if a key employee dies, the beneficiary receiving the key employee's account balance is counted as a key employee.

Perhaps the best way of putting the pieces together is to run through an illustration (table 1). Medical Practice, P.A. has three physicians. Drs. A and B each own 50% of the stock of the practice and therefore are key employees. Dr. C recently joined the practice and does not yet own stock or participate in the management of the practice. The practice has employed the same receptionist, a bookkeeper and two nurses since opening. In 1979 the practice established a money purchase pension plan with an annual employer contribution rate of 10% of compensation. All employees are eligible to participate from their date of employment. Plan assets have appreciated at a rate of 10% per year compounded annually. Employees have not contributed to the plan.

On the December 31, 1983 determination date Drs. A and B's accounts total $123,365.14. Since this is more than 60% of all employees' accounts, the plan is a top-heavy plan.

III. Consequences

As you can see from the example, a typical medical practice, with a small number of employees and a significant disparity between the physicians' and staff's salaries, is likely to have a top-heavy plan. The consequences of having a top-heavy plan are numerous. Some of the requirements of such plans affect all employees while others affect only key employees. In general, a top-heavy plan will be more expensive to maintain and offer less tax deferral to the physicians covered by the plan than a plan that is not top-heavy.

A. Vesting

The first requirement for a top-heavy plan is that it must adopt one of two vesting schedules. One choice is three-year vesting. Under this option all employees who have three years of service with the employer will have a nonforfeitable right to the portion of their accounts or accrued benefits derived from employer contributions. (Of course, an employee is always 100% vested in amounts derived from the employee's contributions.) The plan can exclude employees with less than three years of service from participation in the plan if it has three-year vesting, but as soon as employees participate they are 100% vested in employer contributions. The second type of vesting is six-year graded vesting. An employee is 20% vested after 2 years of service

Table 1

Employee	*Employment Date*	*Annual Compensation*	*Account Balance (Assuming Contribution and Appreciation of 10%/yr.)*
Dr. A	1/1/78	$100,000	$ 61,682.57
Dr. B	1/1/78	100,000	61,682.57
Dr. C	1/1/83	45,000	4,500.00
Nurse X	1/1/78	15,000	9,252.39
Nurse Y	1/1/78	15,000	9,252.39
Receptionist	1/1/78	10,000	6,186.26
Bookkeeper	1/1/78	10,000	6,168.26
Total			$158,706.44

and adds 20% per year of service until he is 100% vested at the end of six years. Which schedule you will want to adopt largely depends on your employee turnover rate.

Either of these vesting schedules probably favors employees more than most non-top-heavy vesting schedules. The effect of top-heavy vesting is to make a plan more expensive to the employer by reducing forfeitures. Forfeitures by employees who leave employment before being completely vested are redistributed among the remaining employees' accounts and generally reduce the employer's cost by reducing the amounts the employer must contribute to the plan.

B. Minimum Benefits

A top-heavy defined contribution plan requires minimum annual contributions on behalf of a non-key employee equal to the lesser of 3% of the employee's compensation or the percentage of compensation contributed on behalf of key employees. A top-heavy defined benefit plan requires minimum annual contributions in an amount sufficient to provide certain minimum accrued benefits for each non-key employee. The accrued benefits must equal an annual retirement benefit based on a percentage of the employee's average compensation for his five highest-paid years of service. The percentage is the lesser of 20% or 2% per year of service. Years in which the plan was not top heavy and pre-1984 years are not counted in the calculations. If an employer has more than one plan, it need meet the minimum benefit requirement in only one plan.

General plan qualification rules require that a uniform percentage of compensation be contributed or accrued on behalf of each employee, and most physicians who can afford to do so will want to contribute more than the minimum benefit amount on their own behalf. Therefore, most physicians' retirement plans are likely to already meet the top-heavy minimum benefit rules. One danger lies where a plan is integrated with Social Security, that is, where it includes Social Security payments or benefits in its contribution calculation. For example, a defined contribution plan may require no contributions on account of compensation up to the Social Security wage base and 5% contributions on account of compensation over the wage base. However, if the plan is top-heavy, Social Security benefits cannot be included in the minimum benefits calculation and the plan would have to be changed to require contributions of at least 2% of the non-key employees' entire compensation.

C. Annual Compensation Limit

A top-heavy plan must limit the amount of compensation taken into account in calculating contributions or benefits under the plan. For the present, no more than $200,000 of compensation per employee can be taken into account. Thus, a physician covered by a top-heavy defined contribution plan requiring 10% employer contributions can have annual contributions of only $20,000 made to his account even if he earns $300,000 from the practice each year. For the physician in this example to have the maximum annual contribution of $30,000 made on his behalf, the plan would have to require employer contributions of 15% of compensation (15% of $200,000 = $30,000). Of course, the employer would be required to contribute 15% of all covered employees' salaries, thus making the plan more expensive.

D. Plan Distributions

1. "Premature Distributions." A present or former key employee less than age 59½ who receives a distribution from a plan receives a "premature distribution." He will pay a 10% penalty tax on amounts attributable to contributions made on his behalf while he was a key employee in a top heavy plan. The tax will not be imposed in two situations: one, if the employee is disabled to the point of being unable to engage in any substantial gainful activity; and two, if the distributions are in the nature of a dividend to the policyholder of an annuity, endowment, or life insurance contract. The Tax Reform Act of 1984 (TRA) changes this rule effective January 1, 1985. After that date, employees who are or were "5% owners," rather than key employees, will be subject to the 10% penalty tax on all distributions from plans attributable to contributions made on their behalf while they were 5% owners. The same exceptions apply. A "5% owner" is an employee who directly or indirectly owns more than 5% of the stock, stock voting rights, capital or profits interest of the employer.

2. Required Distributions. TRA repealed the TEFRA provisions requiring full distribution of plan benefits to key employees by age 70½ or within their life expectancy. For now, pre-TEFRA law is in effect Effective January 1, 1985, new rules will govern plan distributions. An employee must receive his entire interest by the later of the April 1 following the year he attains age 70½ or the April 1 following the year he retires. Alternatively, a plan must commence distribution by the later of those dates and complete distribution over (1) the life of the employee, (2) the lives of the employee and a designated beneficiary, (3) a period not extending beyond the life expectancy of the employee, or (4) a period not extending beyond the life expectancy of the employee and a designated beneficiary. However, under the new rules, the latest date by which a 5% owner can receive or commence to receive his interest is the April 1 following the year he attains age 70½ even if he has not yet retired.

E. Combinations of Defined Contribution and Defined Benefit Plans

Generally, an employer can contribute more to a combination of defined contribution and defined benefit plans than it can to one or more defined contribution plans or one or more defined benefit plans. As a result, employees receive greater benefits from a combination of plans than they would otherwise receive. However, if one or more of the employer's plans is top-heavy, then the employer may lose the benefit of higher contribution limits that are in effect for a combination of defined benefit and defined contribution plans. First, the employer must test to see if one or more of his plans is "super top-heavy." If the accounts or accrued benefits of key employees in a plan total more than 90% of those of all employees, a plan is super top-heavy. In that event, the employer can contribute no more to a combination of defined contribution and defined benefit plans than it can to one or more defined contribution or defined benefit plans. If the plans are not super top-heavy, but one or more is top-heavy, then unless the plan meets certain increased minimum benefit requirements (which will increase the employer's costs), the employer loses the advantage of combining plans.

IV. Conclusion

As you can see, a quick run-through of the top-heavy plan rules indicates that qualified retirement plans are likely to be less attractive to incorporated practices than they were before TEFRA. However, a qualified retirement plan still offers considerable tax savings while providing funds for retirement. Given the uncertainties of the Social Security system, the latter point has become important. Therefore, despite dire predictions of plan terminations after TEFRA, the qualified retirement plan will survive the top-heavy rules. Don't think, however, that once you have amended your plan to comply with TEFRA, you need do nothing further. Congress enacted two new laws affecting qualified retirement plans this year and once again plans must be amended.

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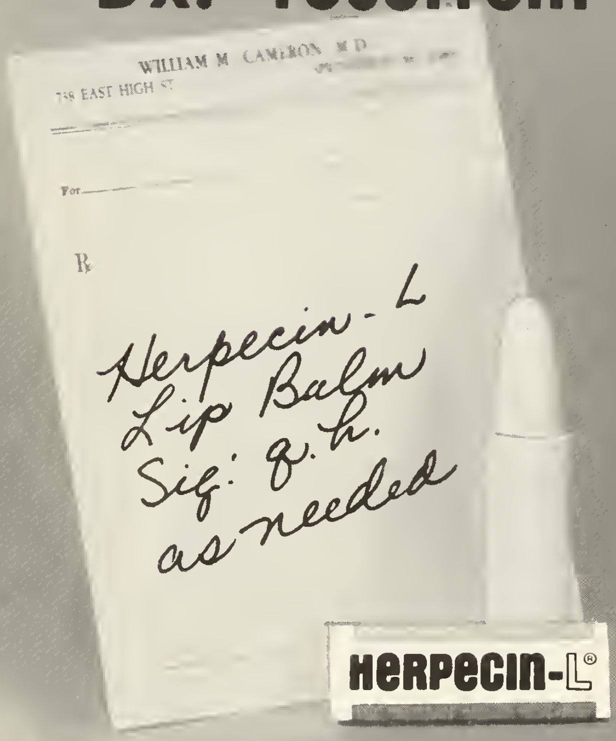

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Julius Seizure — Carbamazepine (Tegretol) Poisoning

Ronald B. Mack, M.D.

• How to care for the patient who took an overdose of CBZ.

WHEN I was a young lad, my peers and I had heroes and heroines; in fact I still do. I don't know if the young people of today have anyone they want to emulate. With some of current celebrities that the youth of our country seem to admire it is hard to see whether these "notables" should be classified as heroes or heroines or, androgynously speaking, both.

Julius Caesar has always been one of my favorite historical figures — a real high achiever, a conqueror of men and, as it turns out, ladies — (three wives and a paramourship with the late, great Cleopatra — the Elizabeth Taylor of her era). During his lifetime, which lasted from 100 B.C. to 44 B.C., he was the Questor in Spain, Aedile, Pontifex Maximus (head of the state religion), Praetor, Governor of Further Spain, a member of the infamous Triumvirate — with the other two members being Crassus and Pompey — Consul and Governor of Cisalpine Gaul, Consul, Dictator and Imperator for life. [A *questor* managed the expenditure of state funds. An *aedile* was in charge of the care of buildings, aqueducts, theaters, saloons, brothels, etc.; a *praetor* was charged with the administration of civil justice; a *consul* was involved in the executive phase of peace and war (a chief magistrate); and an *imperator* was an absolute or supreme ruler.] He was a brilliant military leader and allegedly the second best orator of his time (Cicero won the Academy Award consistently in that department). Caesar performed all these feats even though he was handicapped; fact is, he was an epileptic. It is of interest that Julius' hero was Alexander the Great, another victim of the "falling sickness."

There are several historical references to Caesar's cerebral dysrhythmia, but one of the best, in my opinion, occurs in Will Durant's book *Caesar and Christ*.[1] In this wonderful text it is alleged that at the Feast of the Lupercalia in February 44 B.C., Mark Antony (reportedly drunk and naked) three times offered Caesar the crown of royalty. Three times Julius refused. Then the Roman Senate approached him as he sat in the Temple of Venus and Caesar remained seated. Let me make this perfectly clear — by custom he was supposed to stand up when greeting this august body. Why did he remain in his chair? Many witnesses claim he was overcome by an "epileptic stroke"; other witnesses say he was suffering from a bad case of the "trots" and remained seated to avoid an encopretic episode at so "unpropitious a moment." Another example where Kaopectate might have changed the course of history.

What happened to Julius that day? Did he forget to take his phenytoin or phenobarbital or carbamazepine — nay, nay, I say unto you, he was not taking any anticonvulsants as far as we know. Medicine until the third century A.D. consisted of family herbs, magic and prayer, for gods alone could heal. To ensure recovery the patient prayed to the specific god assigned to his/her specific disease. It is difficult to be historically certain about Caesar's religious beliefs (even though he was the religious head of the area) because he is quoted more than once as saying that no one can alter the plans of the gods, but on the other hand he seems to have been a believer in prophecy expressed through dreams. So much for history. By the way, what were we talking about? Oh yes — carbamazepine (Tegretol) henceforth known as CBZ in this epistle.

Now that the die is cast let us come and see and conquer the problem of CBZ overdose. This drug is structurally similar to the tricyclic antidepressants (oops, could this mean big trouble in overdose?) and is widely used in the treatment of major motor seizures such as grand mal and complex partial seizures as well as the drug of choice for trigeminal neuralgia (tic douloureux) and Lhermitte lightening pain syndrome (how many patients with this have you seen lately?). Apparently the drug works by inhibiting synaptic transmission of neural signals between two thalamic nuclei. The inhibition of the ventroanterior nucleus depresses efferent seizure discharge signals whereas inhibition of the centro-medial nucleus depresses afferent trigeminal pain sensation.

It is useful at this point to review some of the pharmacokinetics (Et tu, Brute?) of Tegretol because it might point the way to the management of the overdose event. After ingestion, the peak serum level is 3-6 hours in newborns, 1 to 8 hours in children and 8 to 24 hours in adults. At therapeutic blood levels (3-12 μg/ml) the volume of distribution (V_D) in newborn infants is 1-2 l/kg and 1-3 l/kg in children. About three-fourths of the plasma CBZ is bound weakly to protein. The metabolism of this drug is mainly hepatic and follows first order kinetics (rate of transfer of

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the drug is directly proportional to the amount of drug remaining). Of the several resultant metabolites only the *epoxide* has anticonvulsant properties. It is important to remember that the elimination half-life (T½) of CBZ and the epoxide ranges from 18 to 54 hours after a therapeutic dose, but only 16 to 26 hours for those patients on chronic Tegretol therapy because CBZ may induce its own metabolism via hepatic enzymes. What is of greater interest to those of us who treat overdose is the fact that the enzymes responsible for the oxidative metabolism of this drug do not seem to be saturable, hence no zero-order kinetics (elimination occurs at a fixed rate regardless of the amount of drug remaining) and thus the T½ is not prolonged in overdose. Chronic use of CBZ can have a profound effect on the metabolism of drugs taken contemporaneously. For example, chronic usage of CBZ decreases the T½ of oral contraceptives, coumadin, phenytoin and clonazepam probably because of microsomal hepatic enzyme *induction*. When ingested with propoxyphene or INH, however, there can be an increased CBZ effect because of microsomal hepatic enzyme inhibition with resulting CBZ intoxication. It has also recently been reported[2] that chronic CBZ ingestion can increase INH-induced hepatotoxicity.

Because Tegretol is structurally related to the tricyclic antidepressant imipramine, it is not surprising that an acute overdose can produce anticholinergic symptoms such as seizures, myoclonus, nystagmus, respiratory depression, ataxia, coma, mydriasis, delayed gastric emptying and tachycardia. The most severe clinical features are CNS depression with respiratory arrest. There is some good news in this otherwise bleak description — recalling only too well that the most common cause of death in most cases of tricyclic antidepressant overdose (not loxapine or amoxapine however) is cardiotoxicity with arrhythmias, etc., it's my pleasure to announce that life threatening cardiac events are only rarely a problem in CBZ overdose. Cardiorespiratory problems can occur of course, usually with serum CBZ levels exceeding 35 µg/ml.

Tegretol has at least one more weird potential property that must be mentioned — it may trigger Giles de Tourette's syndrome in susceptible patients at therapeutic levels of the drug. It has been argued that CBZ has a structural as well as functional structure similar to the phenothiazines and thus may act as a dopamine antagonist. Some investigators suggest that Tourette's syndrome may be the result of an augmentation of dopamine neurotransmission or an alteration in receptor functioning. Therefore in susceptible patients, CBZ acting on altered dopaminergic receptors may trigger the onset or exacerbation of Tourette's syndrome.

The treatment of carbamazepine overdose is fairly straightforward — there are no antidotes and management is mainly supportive, i.e., treat the patient, not the poison. There are some tricks however. Because of the anticholinergic-like action of the drug, delayed gastric emptying is often present with impairment of absorption of the drug. Another fact worth noting is that CBZ can easily form a drug concretion when ingested in quantity in an overdose situation. What this implies to the people who manage such an overdose patient is that gastric emptying is indicated for many, many hours post ingestion, e.g., for as long as 12 hours or more in asymptomatic patients and up to 60 hours in symptomatic patients. Metoclopramide has been used to increase gut motility. *Activated charcoal* can really make a big dent in the absorption of the drug and dramatically reduce the T½ if given repetitively with a saline cathartic. Repeated charcoal and cathartic administration seems to be indicated until the serum CBZ level decreases or there is clinical evidence of improvement. In my recent experience, this type of management works quite well. Fluid diuresis does not work here and is dangerous because CBZ can augment ADH secretion. Hemodialysis and peritoneal dialysis do not appear to be effective in CBZ overdose. Physostigmine has been used to combat the anticholinergic-like effects but this method has been unsuccessful and should probably not be used in this overdose. Charcoal hemoperfusion has been suggested as an option in severely intoxicated patients but experience is very limited with this method.

In Shakespeare's classic work about our hero, there are two characters named Cinna; one is a conspirator who lures Brutus into the plot to eliminate Caesar and the other is Cinna, a poet. The poet is killed on the way to Caesar's funeral. After Mark Antony's funeral oration there is a riot inspired by the speech and the mob confuses our hapless poet with his namesake, Cinna the conspirator. After pleading innocent to the conspiracy charge, the poet is killed by the mob anyway — it is alleged, "for his bad verses." Now that is a frightening prospect. Do not be surprised if my articles are by-lined with a nom de plume from now on. Please be careful out there — the ides of March is soon upon us.

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American Association of Poison Control Centers Certifies the Duke Program: The End of a Long Odyssey

Shirley K. Osterhout, M.D.

• *The Duke Poison Control Center comes of age.*

WHEN Jay Arena organized the Duke Poison Control Center in 1954, life was still relatively simple. This first Center in North Carolina and the second in our country received about 100 calls a year and most of the inquiries were about aspirin. The information in the Center was compiled by Arena and a few of the pediatric residents. The newly organized National Clearinghouse of Poison Control Centers of the U.S. Public Health Service provided without charge excellent and up-to-date card files. Funds from the Department of Pediatrics were used to purchase the half-dozen books on toxicology available at that time. There were no poison control journals.

Arena's secretary and the secretary of the pediatric resident kept the medical record of each case on file cards. There was no paid staff.

By the mid-1960s we were rapidly expanding our information base. There were more available textbooks and books providing product and ingredient information. As our reputation spread as a good information source, not only did our calls increase — requiring the production of more reporting cards — but our written replies to letters resulted in a heavier clerical load. The increased activities added to the cost.

The North Carolina Department of Human Resources, Maternal-Child Health Branch, developed an interest in us and provided funds to the Department of Pediatrics to help with some of the basic needs for 1970-1983. These funds allowed us to develop our own office, hire a secretary, buy a dictating machine, typewriter and file cabinets. All supplies, postage, and telephone bills were paid with these monies. More and more people requested information in the form of pamphlets and brochures and more of these became available — many free, but many had to be purchased. Again, this became a line item in our budget for North Carolina. As our reputation grew, so did the demand for speakers. Each year more invitations were accepted away from Durham to give programs and health fairs. Another addition to the budget was funds for travel. As our services increased so did the State support — up to approximately $40,000 a year until 1980.

During these years the Maternal-Child Health Branch allowed us to survive and grow, while asking very little of us in return. We served as the unofficial state consultant to various agencies and boards. We reviewed written material that came to them and answered letters regarding various phases of toxicology. Each quarter we submitted a financial report and, at year's end, a written report regarding our statistics. Our working relationship with them was pleasant and my opinion of these individuals, especially of Dr. Jimmie Rhyne, cannot be expressed in words.

After several discussions with representatives of the N.C. Office of Emergency Medical Services of the Division of Facility Services, in the spring of 1978 I undertook a "first" for me — writing a grant proposal, which was the first of several to be submitted to them each year. Starting in 1978 and spreading over the next three years, the Office of Emergency Medical Services provided us $130,000. This combined funding, however, proved to be a piecemeal effort toward meeting and maintaining the standards that had now been set forth by the American Association of Poison Control Centers.

We made several applications to the American Association of Poison Control Centers for certification and met all the criteria except two. The first required that the State recognize Duke as a regional center. The State did not wish to designate us as a regional center until we were certified by the American Association of Poison Control Centers. The second requirement was that only "poison information specialists" or "poison information providers" take our calls rather than pediatric resident physicians. The purpose of this is to provide someone whose entire effort is at the disposal of the Poison Control Center.

As defined by the American Association of Poison Control Centers, a poison information specialist is someone qualified to read, understand, and interpret standard poison information resources and to transmit that information in a logical, concise, and understandable way to both health professionals and consumers and to transmit standardized poison center treatment protocols which have been approved by the medical director. This requirement is considered to be met if the person has a degree and/or is qualified for licensure in nursing, pharmacy, or medicine, or equivalent training experience plus training and/or ex-

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From the Duke Poison Control Center, Durham 27710.

perience in toxicology and poison information services. The Association's definition of a poison information provider is exactly the same except that there is no requirement for a degree other than that the person have an appropriate health-oriented background and specific training and/or experience in poison information sciences. We now have poison information specialists and providers who are with us 24 hours a day in all shifts, seven days a week.

The qualifications we have looked for in hiring these people go beyond the definition that the American Association of Poison Control Centers gives, in that we do not want someone who can merely read or give information; we want someone who can also communicate successfully on a personal and caring basis, who can be reassuring to the lay public, who can work in a counseling and training capacity, and who is diligent and reliable. We have advertised and had many applicants for these jobs. I have found that a degree in nursing or pharmacy does not necessarily give one the qualities we are looking for. Some certified emergency technicians who have the qualifications recommended by the AAPCC also meet my own standards. Currently we employ three registered nurses; a pharmacy technician who has worked as a licensed practical nurse and as a Navy corpsman with 20 years of clinical experience in hospitals; two college graduates who are enrolled in the Physician's Assistant school at Duke who are certified emergency medical technicians, one of whom is a certified poison information specialist, having worked at a poison control center in Maine; and a Duke graduate with a B.A. in chemistry who began working with the Center as a data computer technician in 1979 and has proved that bright, non-medical people can be taught and can provide all the qualifications we demand. We have allowed these people to assist outside the Center in nonprofessional training and have encouraged them to take examinations to certify themselves as poison information specialists. A continuing education program is given to them so they will maintain an interest in current changes in toxicology and the treatment of specific problems. They have been trained for their jobs by me and by Assistant Director Richard Drew and have also learned from each other. The starting salary is approximately $8 per hour.

In many ways they are far superior to the pediatric senior residents in that working in the Center is 100% of their job, with no responsibilities at any other outside task. Since their interest is in toxicology, their reading and education are confined primarily to this role so that their knowledge in toxicology is greater than that of the pediatric residents. With no other responsibilities, they are able to take far more time with each call, provide better followup, help review material that might need to be sent to the caller, such as protocols, and arrange transport from one area to another. I have been impressed also by the counseling job they are able to do in the area of poison prevention to the average family as well as counseling in the area of suicide attempts.

Because of financial limitations, Emergency Medical Services was not able to continue our funding at the end of June 1982, and again we had to rely entirely on the Maternal-Child Health Branch of the State Division of Health Services. These funds were minimal compared with what they had been in the past but private funds were found by the Duke University Medical Center Development Office and we remained alive. In January 1983 we received a sizable grant from a private source which enabled us to continue use of our toll-free number and our poison information specialists. We were pleased that what we were trying to accomplish and what we had accomplished were important enough for the private sector to have faith in helping us continue.

In February 1983 a group from Duke Medical Center representing the administration and the Department of Pediatrics met with officials of the N.C. Department of Human Resources, Maternal-Child Health Branch, and Emergency Medical Services. A budget was submitted for what was felt to be the basic needs of the Poison Control Center, which would also satisfy the requirements for certification. A proposal was put together by the staff of the Department of Human Resources under the direction of Dr. Ronald H. Levine to support a statewide poison control center.

In the spring of 1983, Senator Kenneth Royal (D-Durham) filed a bill which was passed by the General Assembly appropriating $360,000 to the Department of Human Resources for the establishment of a statewide poison control and information center. After several months of review, the Department of Human Resources awarded the contract — $180,000 for 1983-84 — to Duke to continue to operate a poison control center and to establish itself as the regional center for North Carolina.

We initiated an outreach program to all hospitals registered with the North Carolina Hospital Association, licensed day care centers, county health departments and community Head Start programs. We have redone the computer program which had been on hold since 1981 for financial reasons and hope we can again achieve an appropriate data collection and instant reporting system for those who need immediate up-to-date statistics. These funds will also help us to enlarge our current poison center library with information not only to cover the most common type of call we receive — that is, for acute exposure — but also to provide information on occupational and environmental hazards, drug interactions, fetal drug problems, and certain consumer issues. We have continued to publish a brochure, *Poison At Work*, and now are also able to provide a small card that can be carried in a wallet or purse or attached near a phone. I feel that one of the best things we can do with this money is to provide information on request to the individual citizen of North Carolina. We have many types of brochures, including material on plants, holiday hazards, pesticides, and even a "poison game" to teach safety to children. Although we have usually tried to accommodate requests from a community to give programs in hospitals, schools or civic organizations, we had been limited in the past several years due to lack of travel funds. We now look forward to such requests. Emergency Medical Services has approved a budget to endorse public education and we are far more available to travel into a community and give programs to both medical professionals and nonprofessional groups. Not a day in February 1984 went by without at least two requests for educational material. Our activities have increased markedly!

In November 1984 Duke was certified as a poison control center by the American Association of Poison Control Centers. Our long odyssey had ended.

We welcome the opportunity to continue to work with the State. We now have the resources to reach the entire State. We can answer questions on acute and chronic exposure and provide information on treatment. Even more importantly, we can move forward in prevention.

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LEARNING WITHOUT WORDS

The Role of Oxygen Pressure in the Fight Against the Chief Killers in the First and in the Last Half of the 20th Century

Barbara Newborg, M.D.

- *The fashionable therapies for tuberculosis patients used earlier in this century had a common physiological effect: they reduced oxygen pressure which in turn inhibited the oxidative processes of the tubercle bacillus.*

WHY were patients with tuberculosis, the chief killer until the 1940s, urged to have maximal weights?

The accepted dietotherapy for patients in the tuberculosis sanitariums consisted in giving large amounts of butter, cream, eggs, cheese and other high caloric items to promote all possible weight gain. The plausible explanation was that, due to the chronic fever, the patients burned up more calories and unless they were overfed they would die of "galloping consumption."

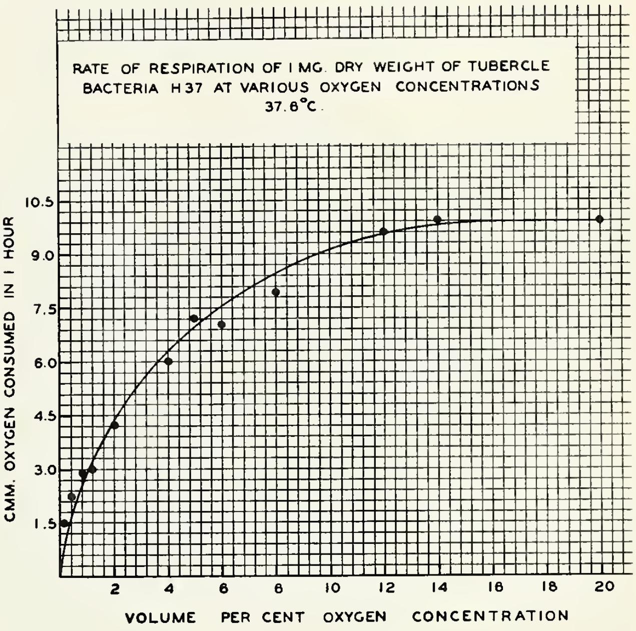
The second fashionable and obviously helpful treatment was sending the patients to high altitudes, the explanation being that the air was purer there and there was more ultraviolet light.

The third type of treatment that had proved successful was pneumothorax, or cutting the phrenic nerve to elevate the diaphragm, or rib resection. The explanation here was that thereby the affected lung tissue was given less work to do and more rest.

After the discovery of antibiotic therapy these forms of treatment were almost relegated to books about the history of medicine. However, from a scientific point of view it was interesting to establish the physiological rationale of these therapies.

In 1939, W. Kempner published a paper about "Oxygen Tension and the Tubercle Bacillus" in the *American Review of Tuberculosis,* in which he reported that contrary to Warburg's "all or nothing law" of cellular respiration, a considerable decrease of the oxidative processes of the tubercle bacillus was found under conditions of lowered oxygen pressure (figure 1).

Since these oxidations are virtually the only energy-supplying mechanism of the tubercle bacillus, its power to harm would be greatly inhibited by conditions like high altitude, pneumothorax, etc., which lower the oxygen pressure at the site of the infected tissue.



But what has this dietotherapy, the insistence on maximal weight, to do with high altitude and pneumothorax?

We have determined* the oxygen pressure in the arterial blood of 105 overweight patients before and after a period on a weight reduction diet. While some of the patients had no complaints except their overweight, quite a few showed symptoms of narcolepsy, lack of alertness, failing memory, impotence, inability to burn calories, etc., which improved with the weight reduction. The outcome of the determinations was an average increase of the oxygen pressure in the arterial blood from 71.1 to 81.4 mmHg after an average weight loss of 49 pounds in an average period of 100 days. (Incidentally, the chest films of obese patients

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From the Department of Medicine, Duke University Medical Center, Durham 27710.

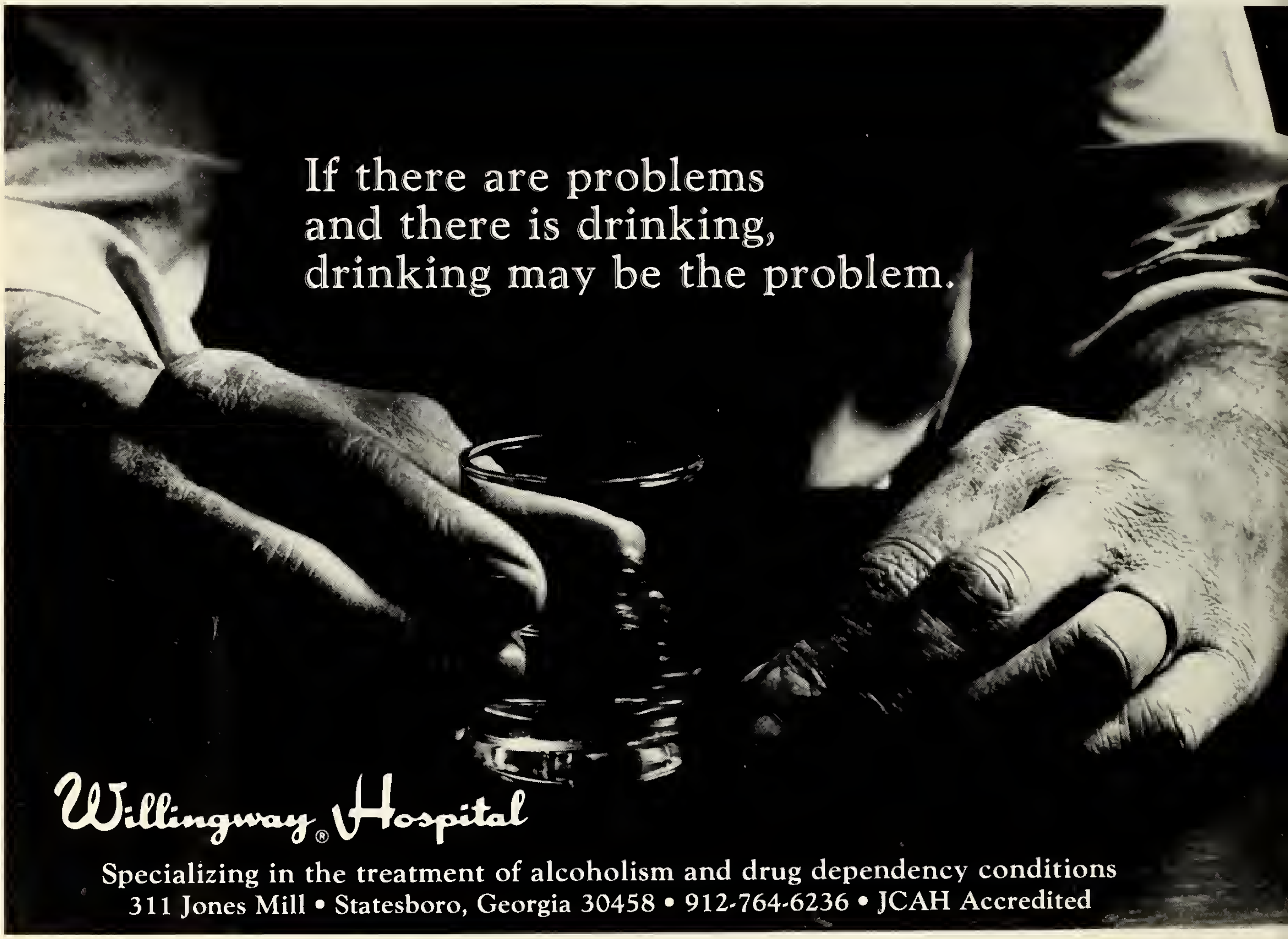
* Barbara Newborg, Fed Proc (Physiology) 1977; 36.

often look like those of patients with bilateral artificial pneumothorax: see *North Carolina Medical Journal,* page 242, April 1983.)

This shows that the practical approach of the dietotherapy of maximal feeding in tuberculosis had the same physiological basis — the decrease of oxygen pressure — as that of high altitude and pneumothorax therapy, though a quantitative explanation was not available at the time it was advised. One is reminded of what E. A. Stead wrote in 1978 in a paper about ''Holistic Health'': ''It is sounder to determine by proper observation whether the treatment is beneficial. If it is, rationale will be developed in time to make the venture fit into the mold of biologic science.''

If the bacteriostatic therapy which we are lucky enough to have now at our disposal did not offer so much better means to kill the tubercle bacillus, the treatment by decreasing the oxygen pressure would probably still be the most efficient.

With regard to tuberculosis, oxygen pressure is no longer of paramount importance. It remains, however, one of the most decisive factors in another therapeutic approach, though exactly in the opposite direction: today we are faced with the task not of *decreasing* but of *increasing* the oxygen pressure in the body in our fight against the chief killer of *our* time, the so-called cardiovascular diseases in which a decrease of oxygen pressure in the cells, for instance by overweight, has occurred, not only in the case of intermittent claudication of the leg muscles but also in the intermittent or permanent claudication of the testes, the kidneys, the myocardium or the brain.



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INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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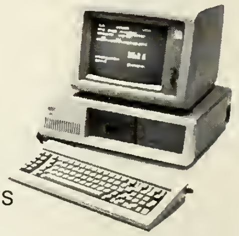

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LEARNING WITHOUT WORDS

Avulsion Injuries of the External Ear

George W. Weston, M.D., J. Connell Shearin, M.D., and Anthony J. DeFranzo, M.D.

- *Even the completely amputated ear can be successfully reattached if it is preserved and brought to the plastic surgeon.*

AVULSION or partial avulsion of the external ear may occur secondary to animal or human bites, motor vehicle accidents, and many other sources of trauma, and it results in a wide variety of disfiguring defects. Although most cases are ultimately treated by a plastic surgeon, the primary care physician, by properly salvaging the avulsed portion, can play an important part in the successful outcome of this injury.

Case Material

Three patients with partially avulsed ear injuries have been treated at Wake Forest University Medical Center in the past 12 months: a 63-year-old man who was thrown from a horse (figures 1 and 2); a 38-year-old woman who was bitten by a horse (figures 3, 4 and 5); and an 8-year-old boy who was bitten by a dog. All three patients were treated within 12 hours of injury by reattaching the avulsed part and burying that part, if needed, beneath a retroauricular skin flap.

Discussion

Since the early 1500s, surgeons have attempted replantation and reconstruction of the avulsed auricle, but only since the 1950s have modern techniques made the results fully acceptable. Techniques for preservation and use of denuded cartilage from the avulsed ear have been advanced by many authors;[1-3] in 1971, Mladick and co-workers[4] first reported success using superficial dermabrasion, reattachment, and pocketing of the denuded cartilage beneath a postauricular skin flap.

The salvage procedure selected by the plastic surgeon depends upon the size and location of the avulsed part, the source of the injury, and the condition of the remaining tissues. Simple replantation of large composite parts will almost certainly fail, and reconstruction should only be attempted by surgeons familiar with the problems that may be encountered.

As in any other avulsion injury, collection and preservation of the avulsed part cannot be overemphasized. Although satisfactory reconstruction can be performed by fabricating a new auricular framework from costal cartilage or contralateral auricular cartilage, salvage of the avulsed segment can greatly simplify the reconstruction and improve the results: The number of surgical procedures required is fewer when the avulsed auricular cartilage is used;

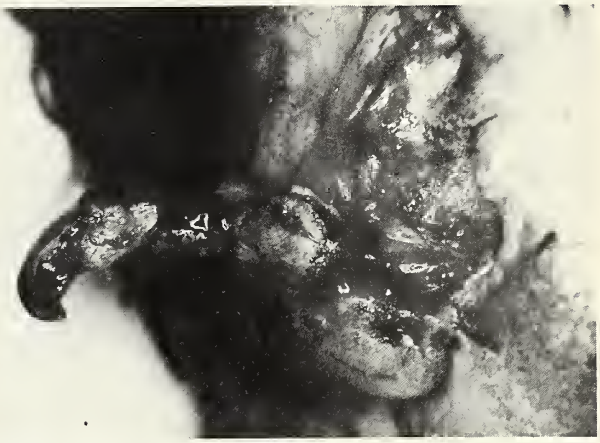

Figure 1. *Near amputation of right helix and scapha in a 63-year-old man who fell from a horse. Blood supply from the inferior pedicle allows viability with simple reattachment.*

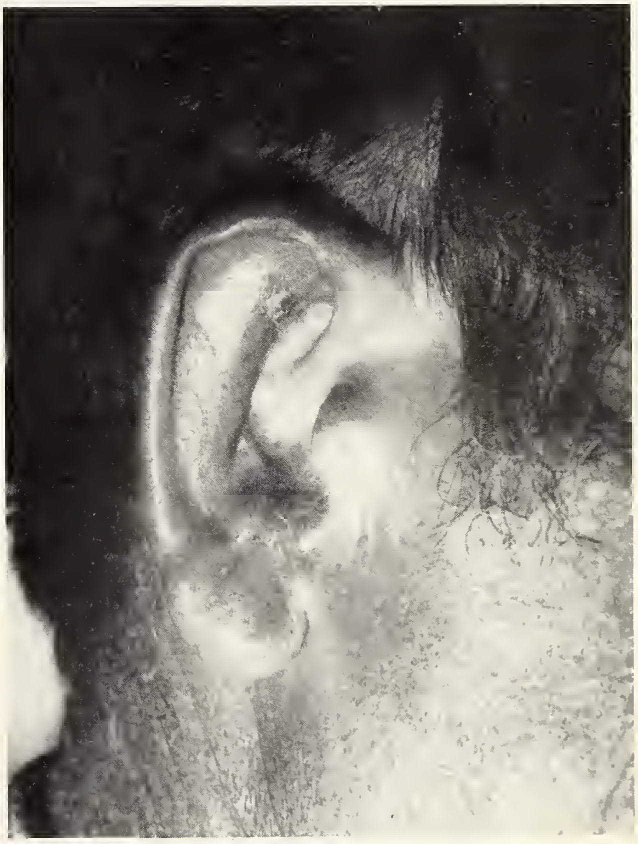

Figure 2. *Result three months after injury.*

From the Section on Plastic and Reconstructive Surgery, Department of Surgery, Bowman Gray School of Medicine, Winston-Salem 27103.

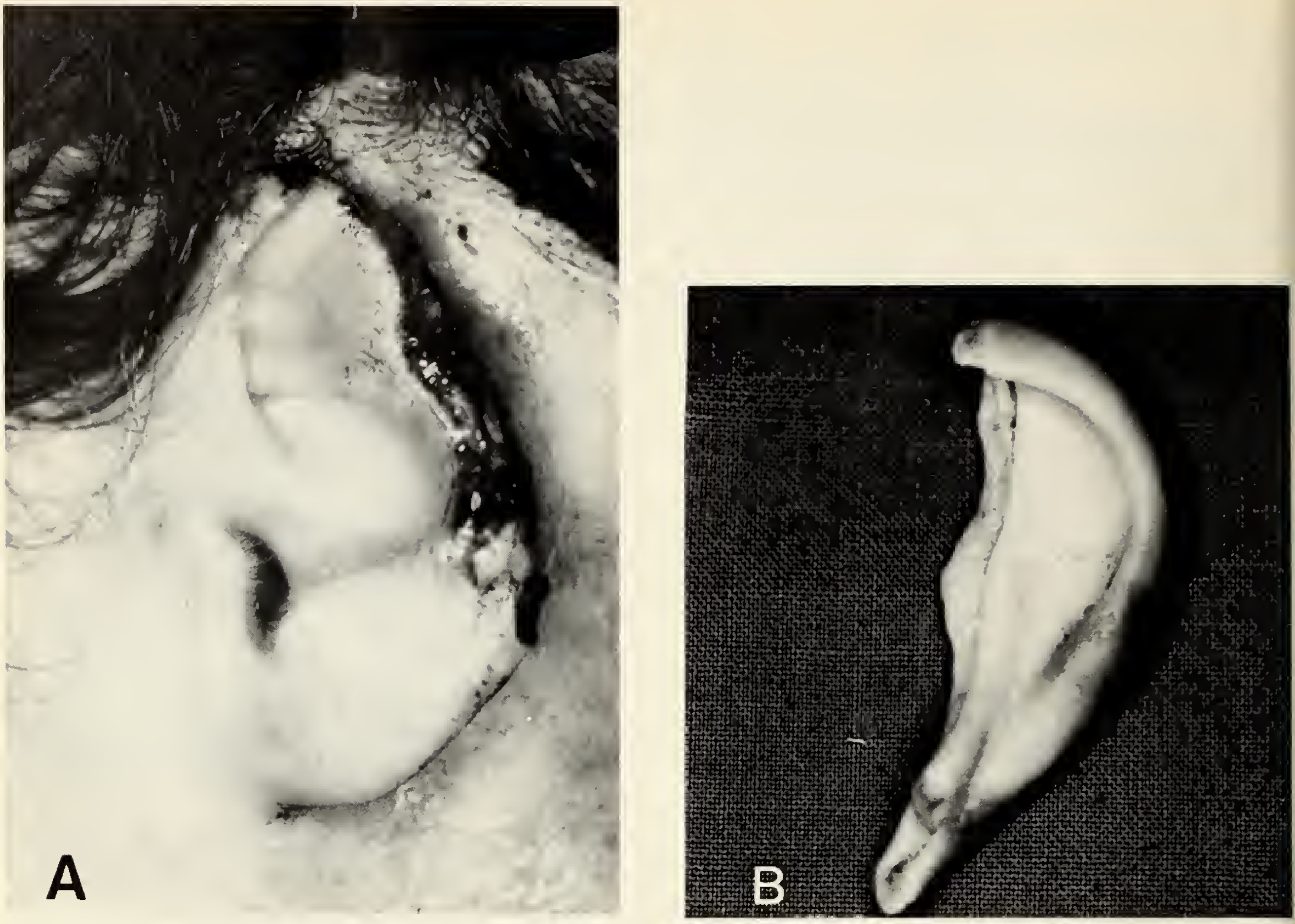

Figure 3 (A and B). *Amputation of the middle and upper half of the left helix and scapha of a 38-year-old woman secondary to a horse bite.*

the ear framework is more delicate; and the result looks more natural.

The retrieved avulsed part should be cleansed of any gross contamination with saline, wrapped in a sterile penicillin/saline sponge, and placed in a polyethylene bag. It should then be placed on regular ice, but separated by a single layer of sterile towel to prevent freezing. Hemorrhage from the site of injury can usually be arrested by application of a bulky pressure dressing. Prophylactic antibiotics such as penicillin or a cephalosporin should be started, tetanus immunization given (or updated if necessary), and adequate analgesia achieved before the primary physician refers the patient to the plastic surgeon.

The plastic surgeon first evaluates the surrounding tissues, particularly the retroauricular area, and then assesses the avulsed part. If the ear remains attached even by a small pedicle of tissue, survival is often possible with simple reattachment (figures 1 and 2). This is not possible if the avulsion is complete (figure 3). With complete avulsion, if the regional cutaneous tissues and the avulsed part are in good condition, the cartilage of the avulsed part is stripped of skin, reattached, and then buried beneath a retroauricular skin flap (figure 4). If retroauricular implantation is not possible because of injury to this area, the cartilage can be "banked" subcutaneously in a cervical pocket, and then transferred to the retroauricular area once wound healing is adequate. Antibiotics are continued for 7 to 10 days. Three to six weeks after the initial replantation, the auricle is elevated with the skin flap attached, and the retroauricular sulcus is created with full-thickness skin grafts. If needed, "touch up" procedures using available local tissues can be performed later under local anesthesia (figure 5).

In summary, reconstruction of the amputated ear is simplified, surgical complications are fewer, and the cosmetic results are improved whenever the amputated part can be preserved and used in the reconstructive surgical procedure.

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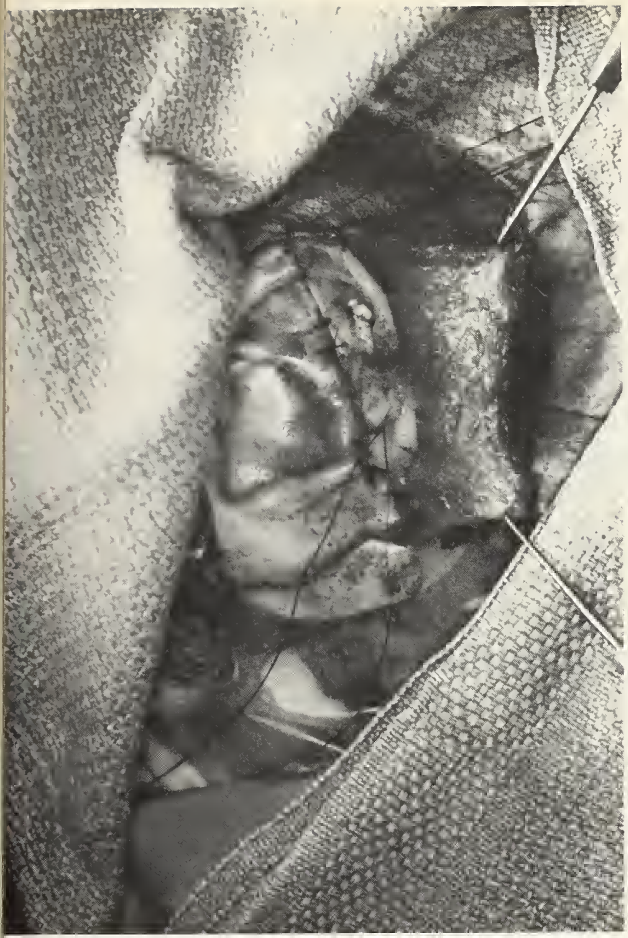

Figure 4. *Replantation of auricular cartilage covered with a ostauricular skin flap.*

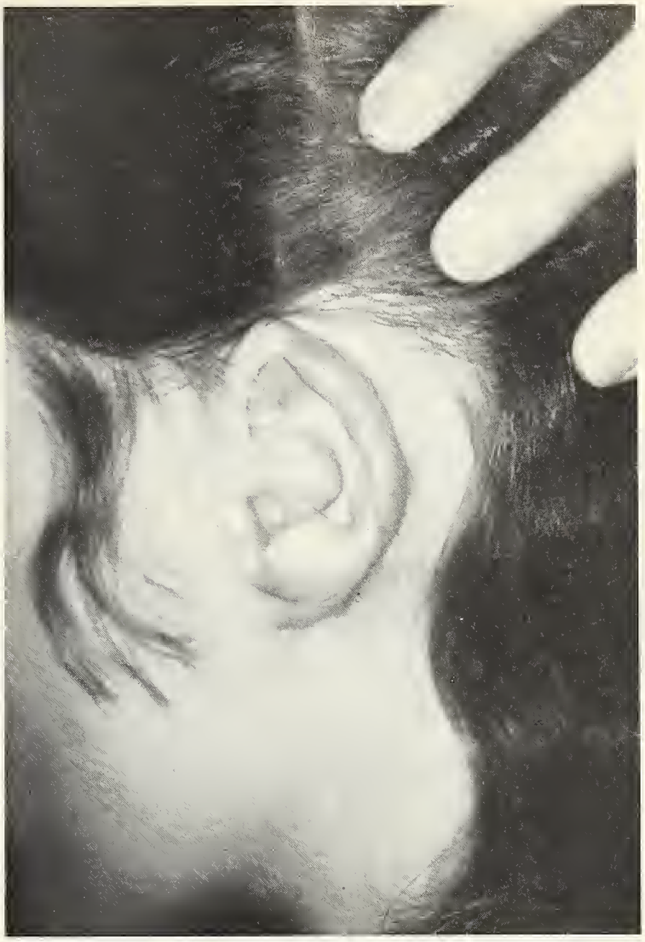

Figure 5. *Final result one year after injury following skin grafting to create the postauricular sulcus.*

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lues" addict might expect from the pentazocine
 a combination of TALWIN Nx and PBZ. When
aken as directed orally, the naloxone component
f TALWIN Nx is inactive. Thus, TALWIN Nx
ontinues to be a safe, effective, oral analgesic for
e relief of moderate to severe pain, now provid-
g added security against misuse.

egistered trademark of Ciba-Geigy Corp for tripelennamine.

Winthrop-Breon

1984 Winthrop-Breon Laboratories

T-540 NDC 0024-1951-04
100 tablets
IV
Talwin® Nx
Each tablet contains pentazocine hydrochloride, USP, equivalent to 50 mg base and naloxone hydrochloride, USP, 0.5 mg.
Caution: Federal law prohibits dispensing without prescription.
Winthrop

Talwin® Nx

IV Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0.5 mg base.

The reformulation of Talwin 50 to Talwin Nx involved the addition of 0.5 mg naloxone to help prevent misuse by injection.

Please see following page for Brief Summary.

Talwin® Nx Ⓘⓥ

Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0 5 mg base

Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone

> TALWIN® Nx is intended for oral use only Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances. (See **Drug Abuse and Dependence** section.)

Warnings: *Drug Dependence* Can cause physical and psychological dependence. (See **Drug Abuse and Dependence**) *Head Injury and Increased Intracranial Pressure* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention; these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure Can obscure the clinical course of patients with head injuries, in such patients, use with extreme caution and only if deemed essential *Usage with Alcohol* Due to potential for increased CNS depressant effects, alcohol should be used with caution. *Patients Receiving Narcotics.* Pentazocine is a mild narcotic antagonist Withdrawal symptoms have occurred in patients previously given narcotics, including methadone *Certain Respiratory Conditions.* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis

Precautions: *CNS Effect* Use cautiously in patients prone to seizures, seizures have occurred though no cause and effect relationship has been established Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours. Such patients should be very closely observed and vital signs checked, if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur. *Impaired Renal or Hepatic Function* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects, it should be administered with caution in renal or hepatic impairment. In long-term use, precautions should be taken to avoid increases in dose by the patient *Biliary Surgery* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures, the clinical significance of these findings is not yet known *Information for Patients* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants. *Myocardial Infarction* Use with caution in patients with myocardial infarction who have nausea or vomiting *Drug Interactions. Usage with Alcohol.* See **Warnings.** *Carcinogenesis, Mutagenesis, Impairment of Fertility* No long-term studies in animals to test for carcinogenesis have been performed *Pregnancy Category C.* Should be given to pregnant women only if clearly needed *Labor and Delivery* Use with caution in women delivering premature infants Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown *Nursing Mothers* Caution should be exercised when administered to a nursing woman *Pediatric Use* Safety and effectiveness in children below the age of 12 years have not been established

Adverse Reactions: *Cardiovascular* Hypotension, tachycardia, syncope *Respiratory* Rarely, respiratory depression *CNS Acute CNS Manifestations* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted *Other CNS Effects.* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor *Gastrointestinal* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress *Allergic* Edema of the face, dermatitis, including pruritus, flushed skin, including plethora *Ophthalmic* Visual blurring and focusing difficulty *Hematologic.* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia *Other* Headache, chills, insomnia, weakness, urinary retention

Drug Abuse and Dependence: *Controlled Substance* TALWIN Nx is a Schedule IV controlled substance

Dependence and withdrawal symptoms have been reported with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient. Tolerance to the analgesic effect is rarely reported; there is no long-term experience with oral use of TALWIN Nx

The amount of naloxone present (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine, however, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals

Overdosage: *Treatment* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered For respiratory depression, parenteral naloxone is a specific and effective antagonist.

Please consult full product information before prescribing

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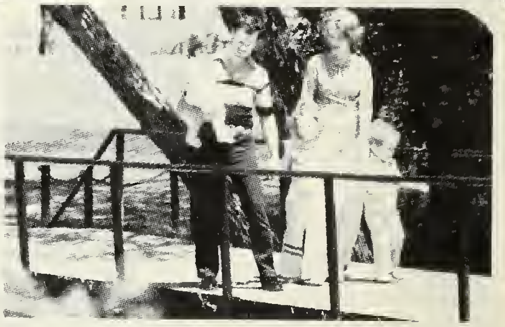

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Continuing Medical Education

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IN STATE

January 7-March 1
Postgraduate Course in Medical Sonics
Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: James F. Martin, M.D., Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 23
Wills, Trusts and Estate Planning for the Physician and Family
Place: Sanford
Credit: 2.5 hours Category I AMA
Info: R. S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

January 26
Sixth Annual Pulmonary Disease Update
Place: Greenville
Credit: 6 hours Category I AMA
Fee: $60.00
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

February 6
Grief Process in Children
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winson-Salem 27101-2482. 919/723-3571

February 13
Anxiety Disorders
Place: Greenville
Fee: $30
Credit: 3.5 hours
Info: Mary Valand, Box 7224, ECU, Greenville 27834. 919/758-5200

February 17-20
Improving Residency Rotations: Curriculum Planning and Negotiations
Place: Rougemont
Credit: 20 hours Category I AMA, AAFP
Info: Dr. Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

February 18-20
Selected Topics for the Practicing Clinician
Place: Durham
Credit: 24 hours Category I AMA, AAFP
Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 6
Eating Disorders of Childhood and Adolescence
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-3571

OUT OF STATE

January 17-19
Advanced Ultrasound Seminar
Place: Orlando, FL
Credit: 14 hours Catetory I AMA
Info: James F. Martin, M.D., Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 22
38th Annual Stoneburner Lecture Series: Rehabilitation Medicine
Place: Richmond, VA
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

January 25-27
Winter Conference on Geriatrics
Place: Hot Springs, VA
Credit: 10 hours AAFP prescribed
Fee: $100
Info: NC Academy of Family Physicians, Box 20146, Raleigh 27619

January 26-31
Dermatology for Non-Dermatologists
Place: Cancun, Mexico
Info: Division of Dermatology, Box 3135, Duke University Medical Center, Durham 27710. 919/684-2504

January 27-February 2
Surgical Management of Malignant Disease
Place: Vail, CO
Credit: 25 hours Category I AMA
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

February 3-8
Selected Topics in Internal Medicine
Place: Snowshoe, WV
Credit: 20 hours Category I AMA and AAFP
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878

February 3-8
Sports Medicine for the Primary Care Physician
Place: Snowshoe, WV
Credit: 20 hours Category I AMA and AAFP
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878

February 4-6
Winter Retreat: Pulmonary Medicine
Place Wintergreen, VA
Fee: $250
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

February 16-23
Radiology Postgraduate Course
Place: Ixtapa, Mexico
Credit: 25 hours Category I AMA
Info: Jackie Wright, Box 3834, DUMC, Durham 27710. 919/681-2711 ext. 285

February 24-28
Duke Aging Symposium
Place: Palm Beach Gardens, FL
Credit: 15 hours Category I AMA
Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 4-7

Interventional Techniques and Radiologic Management of the Emergency Patient

Place:	Williamsburg, VA
Fee:	$425
Info:	Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 16

Reconstructive Plastic Surgery

Place:	Richmond, VA
Info:	Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 29-31

Ophthalmology: Cataract Surgery and Intraocular Lenses

Place:	Williamsburg, VA
Fee:	$275
Info:	Kay Parrott, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

New Members

BUNCOMBE

William Maurice Huffstutter (CHN), 50 Doctor's Drive Ste. 210, Asheville 28801

CUMBERLAND

Catherine Herlihy Beyer (PD), 1213 Walter Reed Road, Fayetteville 28305

John Frederick Blue, Jr. (FP), 4092 Professional Drive, Hope Mills 28348

Paul Sheldon Johnson (P), 302 Thorncliff, Fayetteville 28303

DURHAM-ORANGE

Frederick Barton Askin (PTH), Surgical Pathology, Box 27, N. C. Memorial Hospital, Chapel Hill 27514

Michael Bryan Caveness (Student), 107-A Tall Oaks Road, Chapel Hill 27514

James Norman Davis (N), Neurology Section, Durham V. A. Medical Center, Durham 27705

Fred Daniel Koch (Student), 3207 Myra Street, Apt. H, Durham 27707

James Edward Lowe (CDS), Box 3954, Duke Univ. Med. Ctr., Durham 27710

Richard Lucas McCann (GS), Box 2990, Duke Univ. Med. Ctr., Durham 27710

George William Rozakis (Resident), 2 Abingdon Way, Durham 27707

FORSYTH-STOKES-DAVIE

Joseph MacDonald Ernest, III (OBG), Dept. of Ob-Gyn, Bowman Gray School of Medicine, Winston-Salem 27103

Robert Glenn Hornbeck (Student), 1900 Queen Street Apt. A-7, Winston-Salem 27103

Billy Ray Hunter, P. O. Box 2648, Winston-Salem 27102

William Sherwood Kelly (FP), 2031 Academy Street, Winston-Salem 27103

Donald Kenneth Matthews (Student), 1900 C-4 Queen Street, Winston-Salem 27103

GUILFORD

Philip Jerome Karam (FP), 439 W. Swannanoa Avenue, P. O. Box 1477, Liberty 27298

HALIFAX

James Russell Dykes (FP), Route #1, Box 287, Roanoke Rapids 27870

JACKSON

James Clayton Smallwood (OBG), Eastgate Medical Building, Sylva 28779

LEE

Roger Wilbert Anderson (OTO), 1911 K. M. Wicker Drive, Sanford 27330

LENOIR-GREENE

Roy Nathan Everett (PUD), 109 Airport Road, Kinston 28501

MECKLENBURG

John McNeill Gibson (IM), 1029 Churchill Road, Box 207, Davidson 28036

Arlene Rae Martone (OBG), 1012 S. Kings Dr., Ste. 306, Charlotte 28283

NEW HANOVER-PENDER

Boyd Keith Bresnahan (P), 2023 South 17th Street, Wilmington 28401

ONSLOW

Richard Grant Smith (OTO), 124 Epworth Drive, Jacksonville 28540

Larry Brent Wilshire (OPH), 264 Memorial Drive, Jacksonville 28540

PASQUOTANK-CAMDEN-CURRITUCK-DARE

Paul Andrew Kizen (OBG), 1142 N. Road Street, Elizabeth City 27909

PITT

Bela Laroia Aneja (Resident), 210 Churchill Drive, Greenville 27834

Roberta Skinner Gray (PNP), Dept. of Pediatrics, ECU School of Medicine, Greenville 27834

Robert Willard Olds, Jr. (P), 3005 Briarcliff, Greenville 27834

Mark Lucas Phillips (IM), Dept. of Medicine, ECU School of Med. Room 389, Greenville 27834

Jose Miguel Risco (OPH), 107 Lord Ashley Drive, Greenville 27834

ROWAN

George Raymond Everhart, III (FP), 201 Woodson Street, Salisbury 28144

VANCE

Young Hwan Ko (AN), 2131 Coleman Place, Henderson 27536

WAKE

Barry Alan Bruggers (OBG), 121 Edinburgh South, #103, Cary 27511

Timothy Bertrand Hart (IM), 1212 Cedarhurst Drive, Raleigh 27609

James Arthur Mong (OBG), 100 S. Boylan Avenue, Raleigh 27603

Rafael Mariano Moreschi (IM), 530 Loch Ness Lane, Cary 27511
Joseph Walter Sledge, III (IM), 1157 Executive Circle, Cary 27511
Pamela Joyce Whitney (N), 3320 Executive Drive, Raleigh 27609

In Memoriam

WILLIAM K. NELSON, M.D.

Dr. William K. Nelson was born October 16, 1944 and died June 5, 1984. He is survived by his wife Camille, sons Doug and Jeff, and mother Jane. Dr. Nelson's dedication to his profession and patients was absolute. His caring and concern for his patients was exemplary. In return, he was loved by those he cared for.

He loved sports, and was a sportsman in the truest sense. He loved and studied the game of golf, and was a tough competitor on the squash courts. He was a Wake Forest graduate and followed Wake sports with the enthusiasm of a diehard.

Dr. Nelson was an active member of the Centenary United Methodist Church. He lived his faith every day, and offered it to those in need. His home was a place of love, caring, and sharing. He was a wonderful father and devoted husband.

JAMES THORNTON PROCTOR, M.D.

James T. Proctor, M.D., Medical Director of the Child Guidance Clinic, died on February 4, 1984, after a brief illness at the age of 62.

Born in Blytheville, Arkansas, on November 20, 1922, he received his M.D. degree from the University of Kansas. He was serving as a Naval Officer on the U.S.S. Wright at the close of World War II. His residency in Psychiatry was completed at the U. S. Naval Hospital in Philadelphia, Pennsylvania.

Dr. Proctor had a strong interest in education (especially of medical professionals) throughout his career, with positions over the years as an Assistant Professor of Psychiatry at the University of North Carolina and Clinical Professor of Psychiatry at the University of Oklahoma. He was serving in that role for the Bowman Gray School of Medicine at the time of his death.

Dr. Proctor had a deep and abiding concern for children of all ages. He served as Medical Director of the Children's Medical Center in Tulsa, Oklahoma, prior to coming to Winston-Salem. He served in the role of Medical Director at the Child Guidance Clinic in Winston-Salem from 1973 until his death.

His wife, Bobbie Lee Hilton Proctor, died in 1968. Dr. Proctor is survived by two sons: Kirk and Mark Proctor, and by his parents, Cloud Colbert and Hattie M. Garrett Proctor of Overland Park, Kansas.

ROLETTA O. JOLLY-FRITZ, M.D.

Dr. Roletta O. Jolly-Fritz, physician and psychiatrist, age 87, died in Greensboro on August 30, 1984. Born in Marion County, Iowa, September 17, 1896, she grew up on her parents' farm with her three younger brothers. During her childhood she often accompanied her grandfather, Lafayette Jolly, M.D., on his house calls by horse-drawn buggy and decided she would be a physician.

She attended the State University of Iowa, receiving her B.A. in 1921, and her M.D. from the College of Medicine in 1923. After further study at Iowa Psychopathic Hospital, Dr. Jolly-Fritz received her license as a psychiatrist. She had a long medical career which included private practice, work at Central State Hospital in Nashville, Tenn., Allentown State Hospital in Pennsylvania, Osawatomie State Hospital in Kansas, the Central Nebraska Mental Hygiene Clinic in Hastings, and the Guilford County Mental Health Center in Greensboro and High Point, N.C. After her retirement from fulltime work in 1979, she continued as a consultant for Guilford County Mental Health Center and for the Mandala Center in Winston-Salem, N.C.

In addition to her professional life, Dr. Jolly-Fritz enjoyed many activities and travels worldwide. She was married in 1925 to Ralph A. Fritz, who preceded her in death by one year, after 58 years of marriage. Surviving are their three daughters, Mrs. Lolita Binford of Tampa, Fla., Mrs. Jolee Robinson of Westbury, N.Y., and Mrs. Marcia Hartman of Bethlehem, Pa.; one brother, Lorin Jolly of Pleasantville, Iowa; and seven grandchildren.

A scholarship fund has been set up in her memory to sponsor women medical students at the University of Iowa. Gifts can be made: University of Iowa Foundation, Roletta Jolly-Fritz, M.D. Scholarship Fund, Iowa City, Iowa 52242.

Study in Process

The Duke University Psychology Department is conducting a study of coping with rape. The research is aimed at understanding the response to rape over time and the relative effectiveness of various coping strategies. Women who have been victims of rape at any time in their lives are appropriate for this study. Participation involves filling out a confidential questionnaire. In exchange, participants will be offered free informational sessions on coping with rape, a free therapy group, a free support group for partners, and referral to individual therapy. All of these services are optional, and participation is strictly confidential. For more information or to receive a questionnaire, please call Dr. Susan Roth, 919/684-3645.

Names in the News

Dr. William L. Wood, a physician in Yadkinville, received the Distinguished Service Award during the North Carolina Public Health Association's 73rd annual meeting in Wilmington, NC. He received the award during the awards banquet on Thursday, September 20, 1984. The Distinguished Service Award is given each year to an individual in recognition of outstanding contributions to public health in North Carolina over a period of years.

Dr. Wood serves Yadkin County Health Department as Medical Consultant. He has made many contributions to public health in Yadkin County by staffing mass immunizations, working in tuberculosis control and supporting the WIC (Women, Infants, and Children) Nutrition program and prenatal clinics.

As cited in his nomination, "the characteristic that above all others distinguishes Dr. Wood and marks him as a caring person," is his love of people. This sensitivity to the worth of every individual with whom he has contact underlies his entire career, and it was the strong motivation that led him into the study of medicine and a career in general practice.

Dr. Wood is married to Polly Hudspeth of Yadkinville. They have five children and eight grandchildren.

The Medical-Dental Staff at Forsyth Memorial Hospital has established an endowment in honor of the hospital's president who retired December 31, 1984 after 16 years as chief executive officer.

The **Harold G. Koach** Memorial Lectureship will attract nationally prominent speakers to the hospital each year to discuss problems facing physicians and administrators, as well as relations between the hospital and its medical staff.

At a banquet honoring Koach on October 26, the staff announced that $15,000 had been contributed to the endowment. Proceeds from the annual event will be used for the hospital as the medical staff designates.

For additional information, contact Bob Tannehill, Community Relations Director, 919/773-3402.

Letters to the Editor

Someone Loves Us

To the Editor:

There can be no better example of the change one person can effect than our *North Carolina Medical Journal*. It has now become one of the most welcomed publications coming across my desk. Many of my colleagues, I find, now share my enthusiasm. The articles are not only timely and topically interesting, but concise, well written, and most remarkably originate here in North Carolina. We are fortunate and grateful to share in your latest enterprise. Thank you.

H. Strawcutter, M.D.
101 West 27th Street
Lumberton 28358

Not Everyone Loves Us

To the Editor:

I tried but as usual failed to endure even the first paragraphs of two turgid articles in your most recent edition, and was about to file it under some banana peels in my Hefty kitchen-sized trash bag, when I noticed a fetching title: Goosey Patients, Relationship to Jumping Frenchmen, Myriachit, Latah, and Tic Convulsif (NCMJ 1984;45:556-558). The author of the article, E. Wayne Massey, successfully demonstrates two things: 1) All of these syndromes are pretty much alike, and 2) You can publish just about anything in the *North Carolina Medical Journal*.

Of particular (or should I say peculiar) interest, though, is the description, circa 1880, by Dr. George Beard, of the Jumping Frenchmen of Maine. French-Canadian they were, lumberjacks, living on Moosehead Lake in Maine. The doctor notes that if two of them were to stand toe to toe and be startled, they would "strike each other simultaneously with severe blows." (Massey's words) Then what happened?

Dr. Beard doesn't say. Not only does he discreetly neglect to tell the reader about the terrible brawl which must have ensued, he never explains how it is that a putatively compassionate man of the healing art could sneak up on a couple of Jumping Frenchmen in such an obviously precarious position and then scare the poor devils into fisticuffs.

As doctors, we must all bear his shame.

Robert Olds, M.D.
ECU School of Medicine
Greenville 27835

The Author Responds:

To the Editor:

Thank you for sharing Dr. Olds' letter with me. He read it, learned from it, had reactions to it, and took time to write the *North Carolina Medical Journal* a reply. I believe that would fulfill an educational process, the purpose of any journal, and my goal in writing.

E. Wayne Massey, M.D.
Duke University Medical Center
Durham 27710

Medical Mystery and the Whistle Blower: Several Responses to and from the Author

To the Editor:

The act of writing the article, as requested, for the *North Carolina Medical Journal* (October, pages 567-575) about my hospital experiences and chemotherapy gave me a great deal of pleasure. It served as a therapeutic release from side effects as well as a kindling of creative fires. It is nice to be back at my desk — this time with an Apple IIe. I would have hated to miss this high-class improvement over my old worn-out typewriter.

In addition, writing for the *Journal* gave me a feeling of honor. To be a published author in this superlative magazine, following articles by skilled physicians, just has to be a red-letter experience. Dr. Craige's lively cartoons added exactly the right note of humor (some of it wry) which helped me through so many of the tough days.

As if this were not enough, there have been numerous telephone calls as well as letters expressing appreciation for the article, some of them from cancer patients, others from relatives or friends of cancer patients. It is a great reward to know that any person, in reading the article, might find a degree of comfort or, perhaps, an affirmation of life beneath, beyond and even because of the ordeal.

With sincere thanks to all of you for giving me the opportunity to share my belief in faith and fun.

Mebane H. Burgwyn
Route 1, Box 424
Jackson 27845

"It was with great interest that I read your excellent article in the recent issue of the *N. C. Medical Journal* relating your experiences and health problems. I certainly commend you on your positive attitude toward your illness, and would have to think it played a great part in your recovery. Having experienced severe illness on several occasions in my life I feel in a position to sympathize with you in what you have experienced; and to rejoice with you in your recovery which I feel, like mine, was a work of the Lord along with that of the physicians."

Robert B. Outland, Sr., M.D.
Rich Square 27869

"It really helps to know someone else has experienced the same thing and come through so well. I am half way now and am looking forward to the final treatment, although I have had far fewer side effects than most. I understand about 'waiting.' Jim and I have about mastered that skill for it is wait, wait and wait! I feel as you mentioned as I look around the waiting room. I feel far better than some and I am most thankful."

Helen Creech

"You have my highest admiration for your extraordinary courage and spirit — and the incredible fact that you kept your sense of humor throughout. I think it was wonderful that you wrote about your treatment and recovery; it will surely offer solace to many who are still suffering and inspiration to all who read it."

Grayce P. Northcross
3626 N. St., N.W.
Washington, DC 20007

Prescriptions

To the Editor:

We were very pleased to read Dr. John A. Ewing's article entitled "Physicians, Prescriptions and Prescription Drugs" in the *NCMJ* October issue (page 669-70). The Drug Enforcement Administration is, of course, quite concerned with the abuse of controlled pharmaceuticals. Time and again these substances surface in emergency room situations and overdose deaths. There can be no doubt that a vigilant, well educated medical community has a positive impact on drug diversion and drug abuse. We feel that Dr. Ewing's treatment of the issue was accurate and on target. Law enforcement efforts will only be successful when they are exercised in tandem with a proper respect for prescription drugs and a prudent attitude during the prescription process.

Thomas V. Cash
Special Agent-in-Charge
Drug Enforcement Administration
Atlanta, GA 30303

Synthroid

To the Editor:

The article "New Wine in Old Bottles" by Francis A. Neelon, which appeared in the June 1984 issue (*NCMJ* 45:398-9), contains several erroneous statements that may mislead your readers.

Dr. Neelon quotes me incorrectly when he states that Synthroid® tablets now contain more thyroxine than they previously did. While Synthroid tablets were reformulated in early 1982, the reformulation involved only inactive ingredients and tablet potency was not changed.

Secondly, radioimmune assay is not used to standardize tablet size. Indeed, this type of assay has never been found to be satisfactory for tablet potency assays. The currently approved USP assay methodology is high performance liquid chromatography. In the case of synthetic levothyroxine, HPLC gives the same value as the older iodine assay. (This is not the case with dessicated thryroid preparations.) Thus, the change in assay method has not led to a change in tablet potency.

Finally, Dr. Neelon states that his patient was taking 0.175 mg per day of levothyroxine. Synthroid tablets have never been manufactured in this size. The medical literature clearly documents that different levothyroxine preparations have differing bioavailabilities and, if Dr. Neelon's patient was getting her prescription filled with various brands, or with generic substitutes, this may account for her changing serum thyroxine level.

David L. Horwitz, M.D., Ph.D.
Medical Director, Travenol Laboratories
Deerfield, IL 60015

The author's response:

To the Editor:

Dr. Horwitz raises three points in reply to my brief report about the reformulation of Synthroid tablets:

1. He states that I was incorrect in inferring from his earlier letter to me that the new formulation of Synthroid tablets contains more thyroxine than did the previous preparation. His earlier letter mentioned only that the tablets were a "newly reformulated product" and did not claim then that the "reformulation involved only inactive ingredients." Despite Dr. Horwitz' assertion that "tablet potency was not changed," several investigators have found that earlier formulations of Synthroid tablets contained only about 80% of the stated thyroxine content[1-3] while the new preparation contains close to 100% of the stated content.[2-5] The reason for the discrepancy is uncertain. Whether Dr. Horwitz' "inactive ingredients" were more active than we suspect or whether some other explanation pertains, it seems clear to me and to others[3, 4] that Synthroid tablets are now more potent than they used to be. I continue to have to lower the dosage I have prescribed for my patients on Synthroid. Like Dr. Hamburger,[3] I wish the manufacturer has told us of the reformulation in advance.

2. I misspoke when I stated that a radioimmune assay was used to monitor tablet content of thyroxin — as Dr. Horwitz points out, an HPLC assay is used. Both are noble techniques, capable of precise and accurate results. I apologize for the error, but continue to applaud the use of better methods to monitor the drug manufacturing process.

3. Finally, Dr. Horwitz points out (correctly) that Synthroid tablets have never been made in a 0.175 mg size and infers (incorrectly) that my patient must have been using bastard forms of levothyroxine to account for the hyperthyroidism she developed on Synthroid. In fact, Synthroid *is* made in 0.15 and 0.025 mg sizes. My patient and I capitalized on the mathematical property of addition by having her take one tablet of each size daily to provide 0.175 mg/day. It was never an ideal solution because nobody likes taking two pills when one will do. That now seems to be a moot point. Since nowadays most of my patients seem to get thyrotoxic on 0.175 mg/day, I rarely have to prescribe the cumbersome two tablet regiments.

Francis A. Neelon, M.D.
Duke University Medical Center
Durham 27710

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Canker Sores

To the Editor:

This is in reference to the article on Canker Sores in the November 1984 (page 719) issue of *NCMJ*. I would appreciate it if Dr. Burton and associates could comment on two observations I have made on this problem.

First, I have found the most effective treatment is the use of the silver nitrate stick. The stick is dipped in water and then directly applied to the ulcer until it turns white. The patient then rinses his mouth with water.

Second, I have seen what might be considered an "epidemic" within a family. As one member gains relief another develops the ulcers. This would strongly indicate a viral etiology or perhaps all members are under the same elements of stress.

Stanley Grosshandler, M.D.
4905 Richland Drive
Raleigh 27612

The author's response:

To the Editor:

We would like to thank Dr. Grosshandler for his observations. Topical silver nitrate, which acts as a caustic, is certainly a therapeutic alternative worth mentioning. Unfortunately, many patients will provide the opportunity to experiment with many of the listed therapies in an attempt to control this miserable and often relapsing condition. We are unaware of careful prospective clinical trials that evaluate the merits of one treatment over the other and would expect that the process of trial and error will establish the best treatment for a given patient. Until the etiology is established, it is unlikely a specific treatment will be available.

Our personal bias is that virus is related to the pathophysiology of oral ulcers in some patients. The epidemic mentioned by Dr. Grosshandler is certainly compatible with that notion and also supports theories of a genetic predisposition. Clusters of cases provide an excellent opportunity to evaluate both possibilities.

Claude S. Burton, M.D.
Division of Dermatology
Duke University Medical Center
Durham 27710

Features for Patients

To the Editor:

For many months I have enjoyed the section in the *North Carolina Medical Journal* on patient information. It is written in a way that patients can quickly comprehend and get a lot out of.

I would like very much to reproduce some of these topics to distribute to certain of my patients. Do you provide reprints? If so, will you please send a price list? Would I have your permission to duplicate some of them myself?

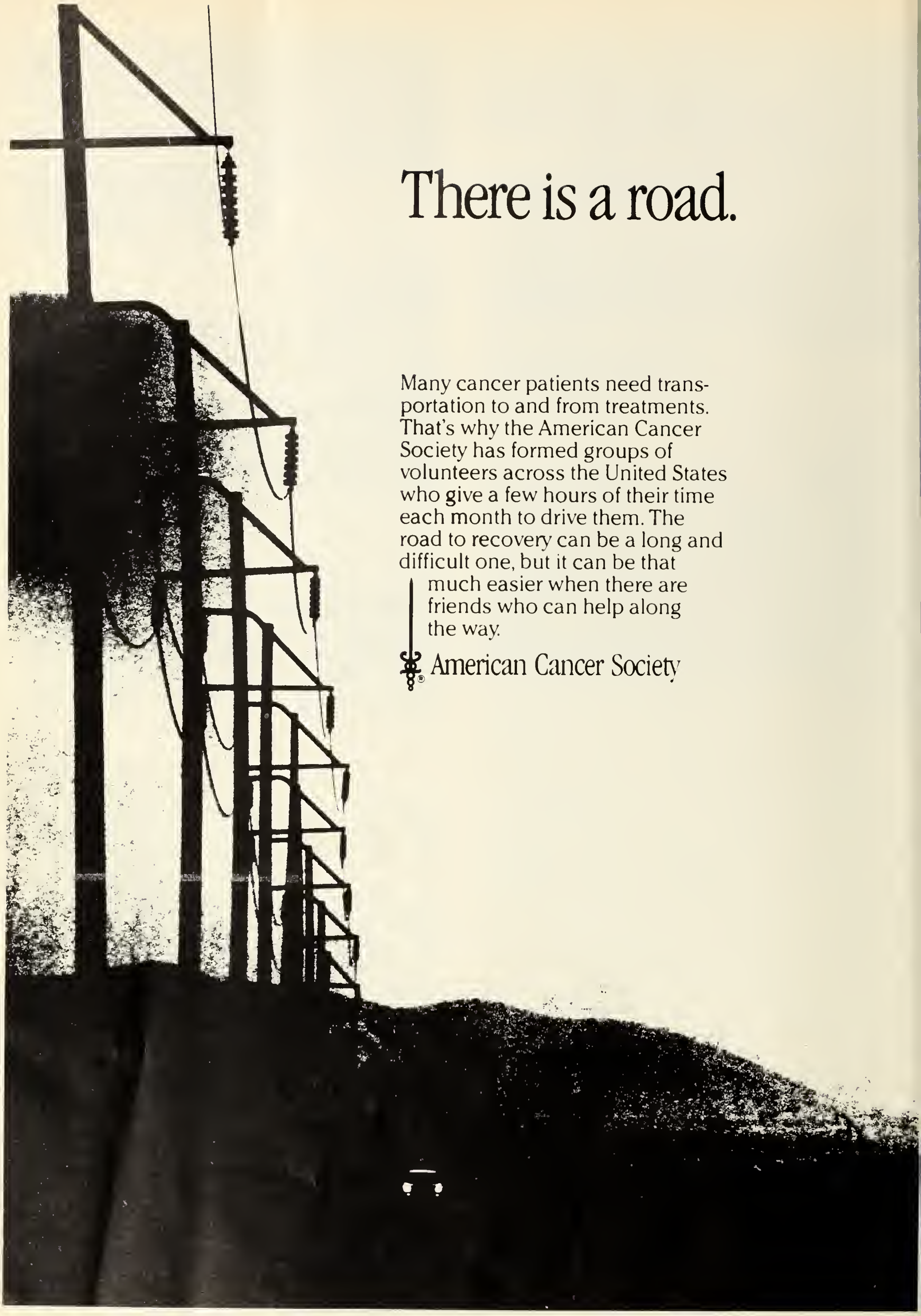
Keep up the excellent work.

C. R. Fernandez, M.D.
Medical Director
Nalle Clinic
Charlotte 28207

The Editor's Response

I appreciate your taking the time to write me about the patient section of the *Journal*. Reprints are not available but you are welcome to duplicate whatever you wish.

Eugene A. Stead, Jr. M.D.



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ABOUT THE COVER: Dr. Allison of East Carolina University initiated the helicopter section for this month's issue when he sent me his paper. He was therefore offered the option of paying for the cost of having the ECU helicopter in color on the front cover. He declined. Duke accepted the opportunity and its helicopter is on the cover. [Photo by Anthony Benson, Division of Audiovisual Education, Duke Medical Center.]

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SCIENTIFIC ARTICLE

Maternal Mortality in North Carolina: A Historical Survey and Current Update

W. Joseph May, M.D. and Frank C. Greiss, Jr., M.D.

- *A five-year update (1976 to 1980) and review of maternal mortality in North Carolina based on 35 years of continuous analysis.*

THE Maternal Mortality Committee was constituted by the North Carolina State Medical Society in 1945. Three thousand seven hundred and eighty maternal deaths have been reviewed and analyzed through the Committee during the 35-year period. Eighty-five maternal deaths studied for five year analysis 1976 to 1980 are reported with a mortality rate of 23 per 100,000 live births. Two deaths complicated 127,332 abortions for a rate of 1.46 per 100,000. Direct and indirect causes of death for the periods 1946 to 1950 and 1976 to 1980 are compared. There has been a 90% reduction in maternal mortality in North Carolina during this 35-year period.

Historical Background

In the early 1940s, North Carolina was a predominantly rural state with a minimum of organized prenatal care. Medical specialists in Obstetrics and Gynecology were limited to the larger cities and the two four-year medical schools then extant. Each year approximately 100,000 live births occurred, two-thirds in the white race and one-third in the non-white races. Over 97% of white deliveries were attended by a physician with 20% occurring at home. While two-thirds of the black deliveries were attended by physicians, about two-thirds occurred at home and half of these were attended by untrained "granny" midwives. It is not surprising that North Carolina's maternal mortality ranked 37th in the United States.

It was on this background that in 1945, Dr. Oren Moore, then President of the North Carolina State Medical Society, constituted a new Maternal Welfare Committee whose initial charge was to study maternal mortality in the state. The prime mover of this idea, Dr. Frank R. Lock of Winston-Salem, who was to become the 14th President of the American College of Obstetricians and Gynecologists, was appointed Chairman of this Committee. Other members of the original Committee were prominent obstetricians-gynecologists from representative areas of the state and included Dr. Robert A. Ross of Durham, the 20th President of American College of Obstetricians and Gynecologists. In cooperation with the State Board of Health, the *modus operandi* of the Committee was to review anonymously case records of maternal deaths and to communicate their findings and suggestions for prevention to the involved physician. Thus, progress was to be by education rather than coercion, a process designed to encourage cooperation by attending physicians. In 1950, Dr. James F. Donnelly of Raleigh became Chairman of the Committee and in 1962 Dr. W. Joseph May replaced him and serves as the leader of the Maternal Mortality Study Project to the present.

Material and Methods

Through December 31, 1980, the records of 3,780 maternal deaths have been reviewed and analyzed. The classification of obstetric causes of death, which may be direct or indirect, recommended by the Committee on Maternal and Child Care of the Council on Medical Service, American Medical Association, is used. This defines a maternal death as "the death of any woman dying of any cause whatsoever while pregnant or within 90 days of the termination of the pregnancy, irrespective of the duration of the pregnancy at the time of termination or the method by which it was terminated."[1] A direct obstetric death is a death resulting from complications of the pregnancy itself, from intervention elected or required by the pregnancy, or resulting from the chain of events initiated by the complications or the intervention. An indirect obstetric death is a death resulting from disease before or developing during pregnancy (not a direct effect of the pregnancy) which was obviously aggravated by the physiological effects of the pregnancy and caused the death. With the cooperation of the North Carolina State Health Department, birth certificates have been cross-checked with death certificates to assure completeness of data collection. Since the advent of elective abortions which now comprise over 25% of conceptions in North Carolina, maternal mortality rates have been expressed as a function of both total live births and total conceptions (live births plus elective abortions). This permits more realistic comparisons with earlier data and with national data.

Results

During the first five years of the study, 1946-50, 532,310 live births and 914 maternal deaths occurred (172

From the Department of Obstetrics and Gynecology, Bowman Gray School of Medicine, Winston-Salem 27103.

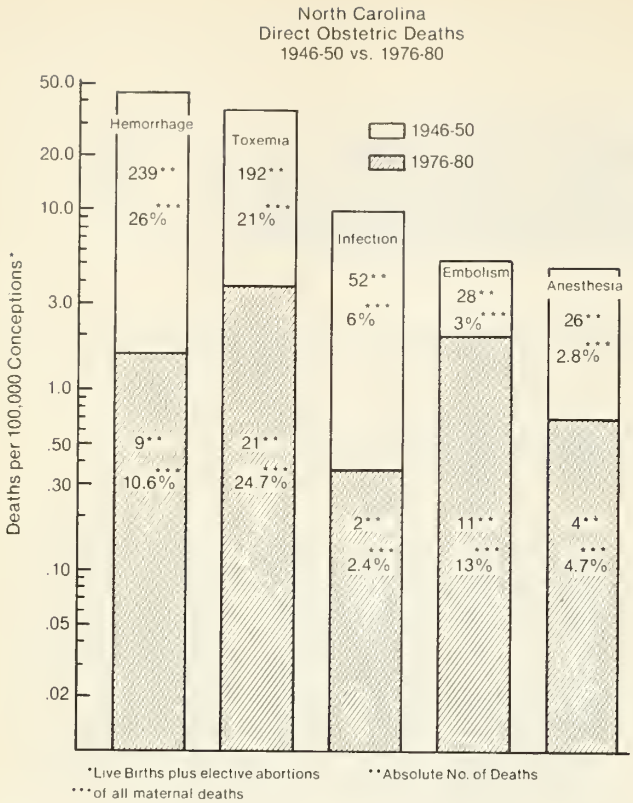

Figure 1. *Semi-log graph comparing distributions of maternal deaths by classification in North Carolina for the periods 1946-50 and 1976-80.*

per 100,000).[2] During the period 1976-80, 369,779 live births, 553,113 conceptions and 85 maternal deaths occurred (23 and 15 per 100,000, respectively). This represents a 90% reduction in maternal death rates during the 35 year period. Distribution of deaths by classification are compared for the two periods in figure 1. Relative to the 1946-50 period, the percentage of deaths from direct obstetric causes have decreased and those from indirect obstetric causes have increased. This distribution has been essentially the same since 1966.

Deaths by classification, major direct causes and race for 1976-80 are shown in table 1. The ratio of non-white to white maternal mortality rates has been surprisingly constant since 1966 varying between 2.62 and 2.72 during each five year period. However, this represents greater than a 50% reduction from the 6.0 ratio extant during the first half of the overall study period. Of the major direct obstetric causes of death, the ratio approaches parity only with vascular emboli (1.4 in 1971-75 and 1.70 in 1976-80).

Table 1
Maternal Death Rates* by Race, Classification and Major Direct Causes, North Carolina, 1976-80

	Non-white	White	Non-white/ White
Direct Obstetric	15.8	4.9	3.23
Hemorrhage	3.8	0.5	7.60
Toxemia	6.5	2.4	2.70
Infection	1.6	0.0	—
Embolism	2.7	1.6	1.69
Anesthesia	1.6	0.3	5.30
Indirect Obstetric	6.5	3.0	2.17
Total Obstetric	26.2	10.0	2.62
Total Obstetric (1971-75)	75.0	27.6	2.72
Total Obstetric (1966-70)	116.9	43.9	2.66

* Deaths per 100,000 conceptions

During 1976-80, two deaths complicated 137,332 elective abortions for a rate of 1.46 per 100,000. The classical maternal mortality rate exclusive of elective abortions was 19.97 per 100,000 live births, 13.7 times greater. One woman died of an amniotic fluid embolism complicating a mid-trimester saline abortion and the other died of lidocaine toxicity during a suction curettage at 10 weeks gestation. The deaths of two additional women first encountered moribund or dead from septic abortions may have been prevented by legal elective abortions.

Direct obstetric causes of death for the periods 1946-50 and 1976-80 are compared in figure 2. Toxemia of pregnancy has been the leading individual cause of death for the past 15 years of the study. Relative to the overall reduction in direct obstetric deaths, those from vascular emboli have not kept pace reflecting most probably the less preventable nature of these complications.

Specific causes of death within generic causal groups for 1976-80 are shown in table 2. The following observations are noteworthy. One-third of the deaths from hemorrhage were from ectopic pregnancy. Two of these could have been prevented had today's rapid and highly sensitive tests for human chorionic gonadotropin been available. Overall

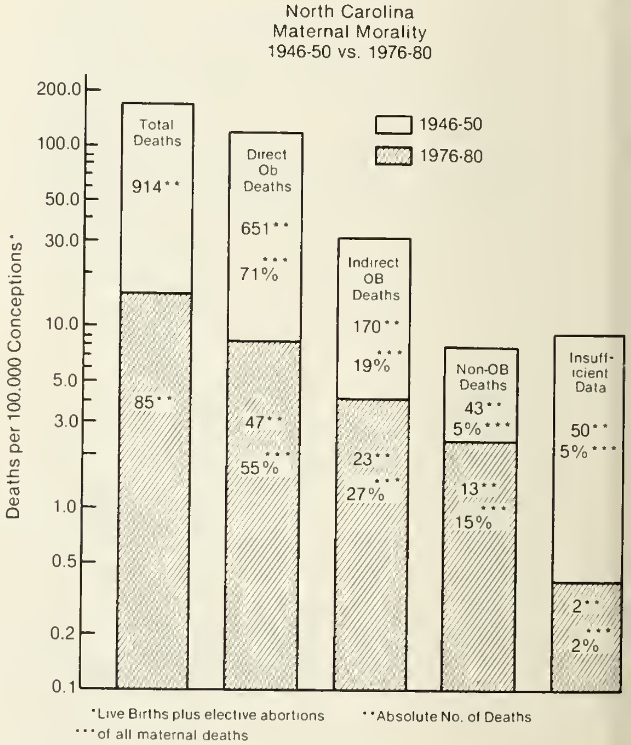

Figure 2. *Semi-log graph comparing major causes of direct obstetric maternal deaths in North Carolina for the periods 1946-50 and 1976-80.*

Table 2
Specific Causes of Maternal Deaths in North Carolina, 1976-80

	No.
Hemorrhage	
Ectopic pregnancy	3
Uterine perforation/rupture	2
Incomplete abortion	1
Placenta accreta	1
Abruptio placenta	1
Postop hemorrhage	1
Toxemia	
Cerebrovascular accident	7
Coma/convulsion	6
DIC/multiple organ failure	4
Renal failure	2
Heart failure	2
Infection	
Septic abortion	2
Embolism	
Blood clot	7
Amniotic fluid	3
Air	1
Anesthesia	
Aspiration	2
Local anesthetic toxicity	2

six of the nine deaths were considered medically preventable. Had the other three patients sought medical care, they too would not have died.

In addition to the classical causes of death from toxemia, disseminated intravascular coagulopathies associated with multiple organ failure have emerged as a significant factor. Usually these women, although seriously ill, were thought stable when without premonitory signs they began a rather sudden inexorable downhill course.

Aspiration of gastric contents continues to be an ever present potential cause of anesthetic deaths in nonpregnant women accounting for 50% of anesthetic deaths in this series.

Indirect obstetric deaths for the two study periods are compared in figure 3. Cardiac disease continues to be the single largest cause of death in this classification. With the exception of three deaths from sickle cell disease, the remaining deaths were from individual rare medical conditions.

Discussion

Those physicians who have participated in North Carolina's maternal mortality study can consider their efforts a factor in the steady decline in mortality rates (figure 4). The obvious medical progress over the past three decades, along with economic and social forces have had major impact on improved health care in general. The increased affluence and education of North Carolina's populace, more rapid transportation and racial integration have increased the desire for and improved access to quality medical care. In particular, legalization of the elective abortion significantly accelerated the decline in maternal mortality rates. This is evident in figures 4 and 5 during the periods 1971-75 and 1976-80, particularly in the curve of deaths from infection.[3, 4] Since 1972, no deaths have been

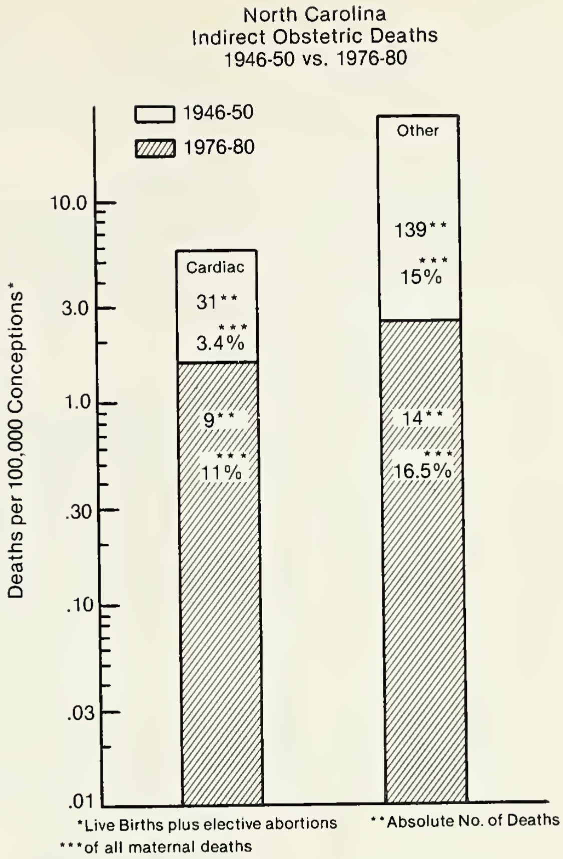

Figure 3. *Semi-log graph comparing causes of indirect obstetric maternal deaths in North Carolina for the periods 1946-50 and 1976-80.*

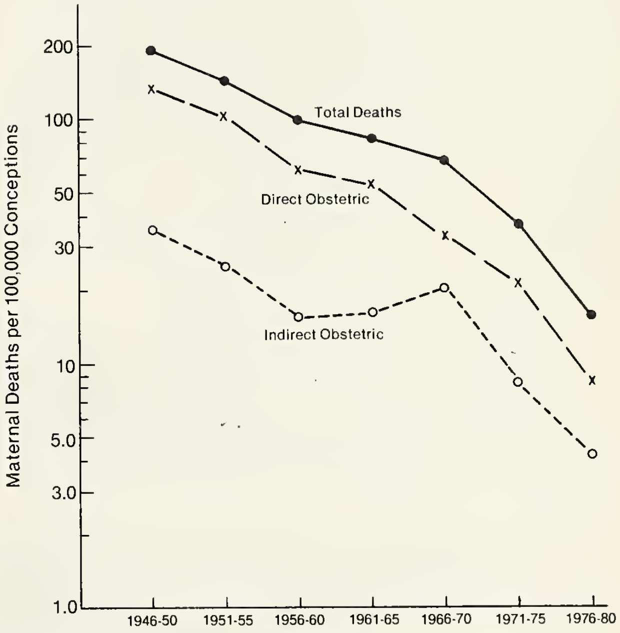

Figure 4. *Semi-log graph of maternal death rates in North Carolina according to major classification from 1946 to 1980 by 5 year cohorts.*

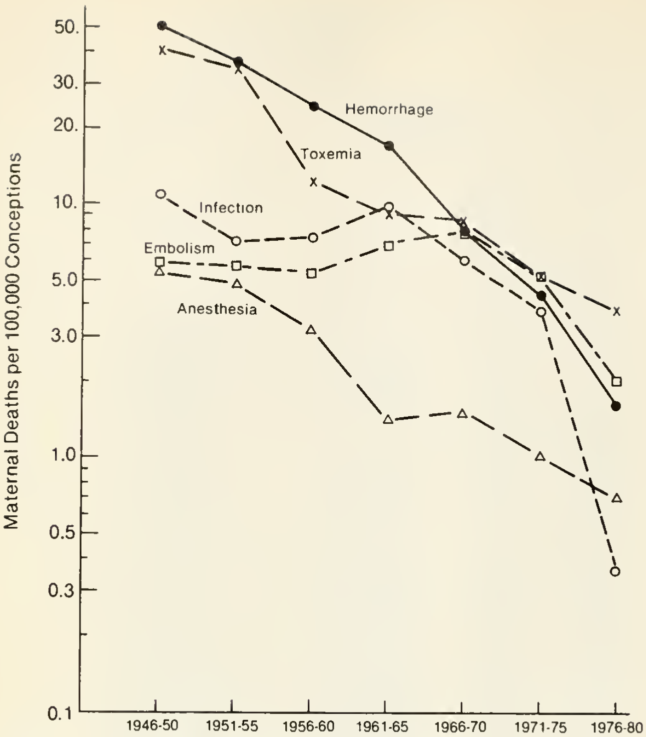

Figure 5. *Semi-log graph of major direct obstetric death rates in North Carolina from 1946 to 1980 by 5 year cohorts.*

attributable to criminal abortions although two deaths in the 1976-80 data are suspect. This is in contrast to eight deaths from criminal abortion during 1971 and 1972, the years immediately preceding the Supreme Court decision legalizing elective abortion.

North Carolina's progress in reducing maternal mortality parallels that of the United States as a whole and that of the South Atlantic region. For the year 1979,[5] North Carolina's maternal mortality ranked 32nd in the nation, changed relatively little from 1945. However, a closer look at these statistics indicates clearly that it is the non-white races that remain at highest risk for maternal mortality. For example, the non-white to white maternal mortality ratios for total deaths were 3.54 nationally and 2.62 for North Carolina. Similar ratios for direct obstetric deaths were 3.17 nationally and 3.23 for North Carolina. These data indicate that future efforts to reduce maternal mortality must focus upon improved education and availability of prenatal care for the non-white races.

Despite the original design of the North Carolina study, it met resistance by some physicians so that during the early phases of the study, paucity of data frequently precluded precise categorization. This resistance gradually diminished but during the past 10 years, the increasingly litigious nature of our society has made many physicians reluctant to make records of such deaths available. The continued support of the North Carolina State Medical Society and interested physicians throughout the state and the maintenance of strict anonymity has allowed accurate data collection. The fact that 65% of patients in the 1976-80 period were autopsied has been of significant value also. However, in today's climate of quality assurance, physicians must become increasingly aggressive in their efforts to further diminish preventable deaths in this very sensitive area. Although the very low maternal mortality rates currently extant and potential legal implications promote little enthusiasm for maternal mortality studies, it is clear that even lower rates are attainable and that new causes of death must be guarded against. For example, at least 20 of the 48 direct obstetric deaths currently reported were preventable, accountability equally distributed between physicians and patients. In addition, today's high technology raises the specter that iatrogenic deaths may be on the rise. This is especially true in the areas of invasive techniques for cardiovascular monitoring and the use of potent beta agonist drugs for inhibiting labor.

The medical profession is becoming more and more accountable for its activities. Under these circumstances, it becomes vital that continued reappraisals of morbidity and mortality statistics are made so that we, the practicing physicians, may remain the determiners of standards of excellence in medical care.

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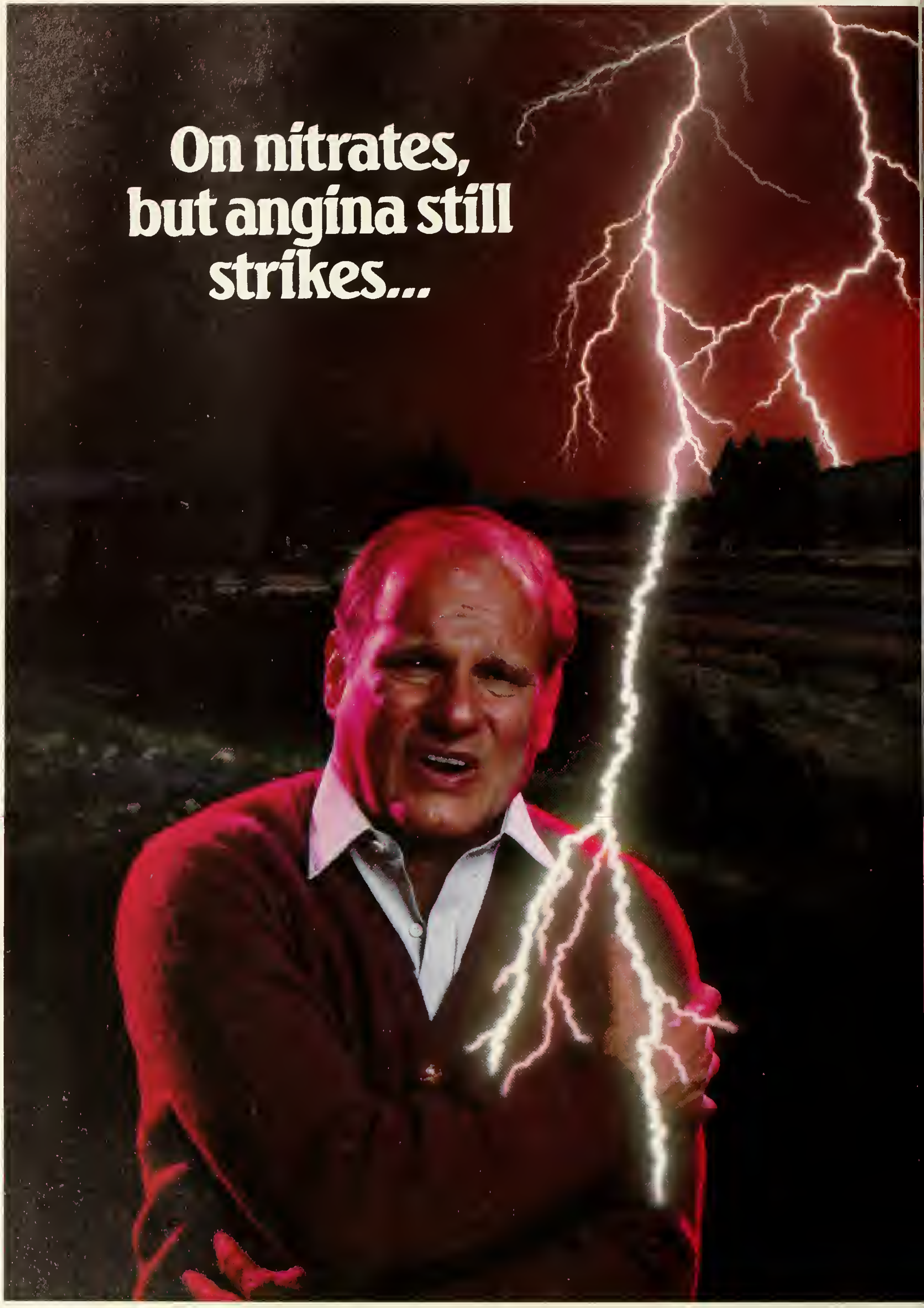
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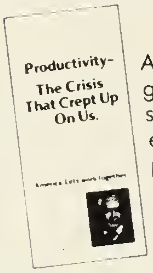
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SCIENTIFIC ARTICLE

The Proper Use of Systemic Fluoride Supplements with Children in Medical and Dental Practices

Steven M. Levy, D.D.S., James W. Bawden, D.D.S. and Ronald H. Levine, M.D.

- *Because children usually do not visit a dentist until age 3 or 4, the physician needs to see that they are introduced to fluoride in proper doses and by appropriate routes as early as possible.*

Introduction

The appropriate use of fluoride remains the best defense against dental caries. This is true despite extensive efforts to develop improved methods of mechanical plaque removal, to develop chemical agents that safely and effectively reduce the cariogenic activity of bacteria, and to reduce the frequency of intake of cariogenic foods by modifying dietary practices.[1] Occlusal sealants are an important new weapon in caries control, but their effectiveness depends heavily on the ability of fluorides to control smooth surface caries. Although the mechanisms by which fluorides exert their caries-inhibiting effects are not fully understood, they are still thought to be:

(1) reduction of enamel solubility;
(2) remineralization of early carious lesions; and
(3) action on plaque bacteria.[2]

There has been greater interest in and understanding of the remineralization process in recent years, showing that many early carious lesions may be reversible if treated promptly and properly with fluoride.

Fluoride products are intended for use either systemically or topically. After the ingestion of systemic fluorides, fluoride is incorporated into the developing tooth structure. In contrast, topical fluorides only work locally on the superficial layers of enamel and on plaque. Methods of delivering systemic fluorides in the United States include community water fluoridation, school water fluoridation, and dietary fluoride supplements. Topical fluorides may be applied professionally or self-applied. They include fluoride solutions and gels (applied in trays or with a toothbrush or applicator), fluoride dentrifices (toothpastes), and fluoride mouthrinses. Also, topical benefits result from drinking fluoridated water or from chewing fluoride tablets. A comprehensive fluoride program may include a systemic form and several topical forms. The systemic and topical modes should not be used in lieu of each other, but should complement each other.

There are many good discussions of these methods of delivering fluorides, including those by Horowitz,[1] Bawden and Stanmeyer,[2] and in the American Dental Association's *Accepted Dental Therapeutics*.[3] Bawden has also written an article detailing a scientific approach to the practitioner's use of topical fluoride products.[4] These references should be consulted for further information.

The purposes of this paper are to explain the need for, and the importance of, systemic fluoride supplements in North Carolina, and to review the proper protocol for supplement use. The article should be helpful to physicians in providing optimum preventive care for young patients.

The Need for Systemic Supplements

Community water fluoridation is recognized as the most efficient and cost-effective method of providing the recommended levels of systemic fluoride for the prevention of dental caries.[5, 6] Unfortunately, approximately one-half of the population of North Carolina (and the United States) drinks water that is not optimally fluoridated.[7] In North Carolina, 84% of the population served by community water systems is receiving fluoridated water (unpublished observation). However, because the state has such an extensive rural population, this figure represents only 49% of North Carolina's total population. In fact, if *all* community water systems were fluoridated, 40% of the state's population would remain without access to fluoridated water.

Alternative sources of systemic fluoride are necessary if more of our children are to be provided the caries preventive benefits of systemic fluoride. North Carolina has been a pioneer in school water fluoridation and it leads the nation in the number of installations. There are presently 133 school fluoridators operating in North Carolina, serving some 52,000 children (unpublished observation). Generally, the water from these fluoridators contains 4.5 parts-per-million (ppm) of fluoride to approximate the fluoride intake that would take place if the children were drinking water fluoridated at the optimal 1.0 ppm all day, every day. The

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From The Department of Human Resources, Raleigh 27602, and The School of Dentistry, The University of North Carolina, Chapel Hill 27514.

students drink the school water only 6-7 hours daily for approximately 180 days per year. Children drinking school water flouridated at 4.5 ppm will experience substantial caries reductions (~40%), particularly in the late forming teeth.[8]

Children drinking water from a fluoridated community system or a school fluoridation system *should not receive fluoride supplements*. Further information about community and school water fluoridation in your area may be obtained from your local dental public health personnel or from the North Carolina Dental Health Section: 919/733-3853. The Dental Health Section also can provide lists of communities and schools in North Carolina that are optimally fluoridated.

Fluoride Supplement Use

For those children who do not drink fluoridated water either at home or from a school fluoridator, the use of systemic fluoride supplements in tablet or drop form is a safe and effective means of reducing the incidence of dental caries.[9-15] In order to receive maximum preventive benefits, we feel that the supplements must be taken daily from birth until age 13.

Several studies have investigated the extent to which fluoride supplements have been used in the United States. National surveys conducted in 1975 and 1982 by the American Dental Association (ADA) revealed that 53% and 60%, respectively, of general practicing dentists prescribed fluoride supplements.[16, 17] In 1978, Margolis and coworkers found that 81% of pediatricians and 63% of family practitioners who responded to their survey prescribed supplements.[18] In a fluoride-deficient area in Texas, 35% of responding physicians reported that they routinely prescribed supplements.[19] The ADA found in 1982 that 79% of responding physicians prescribed fluoride supplements.[17] The results from a recently completed 1984 survey of dentists in North Carolina showed that 78% of general practicing dentists statewide were prescribing fluoride supplements (unpublished observation). These studies have also shown that many providers are not aware of the proper dosage guidelines, the contraindications (e.g., fluoridated water), and the actual fluoride concentrations in the area's water supplies. This is true among both those prescribing supplements and those not prescribing.

The next sections will review in detail the proper protocol for determining whether supplementation is indicated and, if so, the correct supplement dosage to be prescribed.

Supplement Protocol

It is important for children to receive the *appropriate total dose* of fluoride. This can be accomplished only if the physician knows the fluoride levels of the patient's home and other water supplies (e.g., school, day care, etc.). Fluoride levels exceeding the optimal are associated with an increased risk of dental fluorosis (mottling). Although dental fluorosis is primarily an aesthetic concern, moderate to severe cases often involve pitting and other defects of the tooth surface. Therefore, to avoid overdosing, the physician should know which communities and schools in the area are fluoridated and the levels of fluoride concentration (i.e., 1 ppm versus 4.5 ppm).

A separate water sample should be submitted to the N.C. State Laboratory of Public Health in order to determine the fluoride content of each community, school, or individual water supply if the physician does not have *prior specific knowledge* of the level. Because there can be significant fluctuations in well water fluoride content, even in a small geographic area, one *should not* rely on the results of a sample from a different water source, no matter how near.

Water Sampling Procedures[20]

The North Carolina State Laboratory of Public Health will analyze individual patients' water samples for health professionals. The procedure for ordering sample bottles is as follows:

1. Call or write the Laboratory of Public Health specifying the number of fluoride sample bottles required. Address: State Laboratory of Public Health, Division of Health Services, P. O. Box 28047, Raleigh 27611-8047. 919/733-7308.
2. The laboratory will mail you the bottles and report forms. There will be a fee of 50 cents per bottle plus shipping charges; the patient should provide return postage. (The cost is significantly less than the actual cost of the analysis. Similar programs in other states generally charge $2.50-$5.00 per sample.[21-23])
3. In consultation with the parent, the physician or a member of his/her staff should fill in all of the requested information on the report form except the name of the person who subsequently collects the sample and the time when that occurs. The bottle, the form, and the return address label should be placed in the container and given to the parent to take home (or to school, etc.) to collect the sample. The tap should be run for 30 seconds, the bottle nearly filled and firmly stoppered, the address label attached, and the sample mailed.
4. The results will be sent to the health professional indicated on the report form within a week or two after the sample is mailed.

Frequency and Results of Water Sample Analyses

A recent study investigated the frequency, distribution and results of analyses for fluoride content of drinking water samples in North Carolina.[24, 25] There were 1,935 water samples submitted to the State Laboratory of Public Health by North Carolina health professionals between December 1, 1982 and May 31, 1983. Copies of these reports are kept on file by the Dental Health Section which also monitors community and school fluoridation. Table 1 shows the distribution by provider type. Practicing dentists submitted 39% of these samples, 35% were mailed in by physicians, 22% by health department personnel, and 5% of the providers could not be classified.

Table 2 shows that, in comparison with the total numbers of providers practicing in the state, only 8% of the dentists and 3% of the physicians most likely to provide diagnostic and preventive services to children submitted water samples.

Because of the largely rural nature of North Carolina, many providers in fluoridated communities treat patients who reside in nearby nonfluoridated areas. Therefore, most providers treating young children should have occasion to

Table 1
Distribution of Water Samples by Provider Type[24, 25]

Provider	Number	Percentage
Dentists	746	38.5
Physicians	671	34.7
Health Depts.	423	21.9
Unknown	95	4.9
Total	1,935	100.0

Table 2
North Carolina Health Professionals Requesting Water Analysis[24, 25]

Health Group	Number Sampling Water	Number Practicing[26]	Percent Sampling Water
Dentists	156	1984*	8
M.D.s	61	1983*	3
Health Depts.	20	83	24

* Only those most likely to be routinely providing diagnostic and preventive services to children are included. Dentists included are those in general practice and pedodontics and students in dental school. Physicians are in general practice, family practice, and pediatrics. It was not possible to determine how many of these actually treat children. Therefore, these figures are likely overestimates.

Table 3
Supplemental Fluoride Dosage Schedule*
(In mg. of fluoride per day)

	Parts per Million Fluoride in Water Supply		
Age of Child	< 0.3	0.3 to 0.7	> 0.7
Birth to 2 yrs.	0.25	0	0
2-3 yrs.	0.50	0.25	0
3-13 yrs.†	1.00	0.50	0

* Recommended by the Council on Dental Therapeutics of the American Dental Association, by the Committee on Nutrition of the American Academy of Pediatrics, and by the American Academy of Pediatric Dentistry.
† The American Academy of Pediatrics recommends providing tablets through at least age 16.

Table 4
Frequency of Various Fluoride Levels in North Carolina Water Samples[24, 25]

Fluoride (ppm)	Frequency (%)	Supplementation Recommendations*
< 0.3	87	Full
0.3-0.7	6	Reduced
> 0.7	6	None

Note: Fluoride levels greater than 2.0 ppm were found in 1% of the samples.
* See table 3.

assay water for fluoride content on behalf of their patients and prescribe fluoride supplements. Since many more births occurred in nonfluoridated areas than there were samples submitted,[27, 28] either (1) many children in need are not benefiting from fluoride supplements and/or (2) many receive supplements without proper water fluoride assay. Of those samples submitted by dentists, 29 pedodontists provided 44% and one pre-paid dental plan clinic sent in 29%. Thus, a small number of dentists requested most of the assays. A small number of physicians and health departments similarly provided the majority of samples from these sources. Eight physicians submitted 71% of the physicians' total number of samples, and 5 of the 83 health departments submitted 78% of the samples from these departments. Samples were received from 76 of North Carolina's 100 counties, but 53% came from only 9 counties. Clearly, a small number of practitioners in each provider category requested fluoride analyses.

The present guidelines for systemic fluoride supplements recommended by the American Dental Association, the American Academy of Pediatric Dentistry, and the American Academy of Pediatrics are seen in table 3.

The revised pediatric guidelines are now identical to the ADA recommendations except for the age at which supplements may be discontinued.[29, 30] In the past, the different dosage schedules had caused problems because physicians and dentists were not following the same schedule.

As seen in table 3, any water fluoride level greater than 0.3 ppm requires adjustment from the full dosage supplement.

Table 4 shows that 12% of the study samples warranted adjustment.[24, 25] One percent of the samples had fluoride levels exceeding present EPA recommended guidelines for maximum contaminant level, more than twice the optimum level of 1.0 ppm. [To encourage and standardize proper fluoride prescription procedures, the North Carolina Dental Health Section has designated 1.0 ppm the optimal level for all of North Carolina, despite regional temperature differences which would otherwise require minor variations in the optimal level. This designated level of 1.0 ppm is well within the optimal range for all of North Carolina.] Of the 76 counties with at least one sample submitted, 8 counties (11%) had a reading greater than 2.0 ppm, 33 counties (43%) greater than 0.7 ppm, and 47 counties (62%) greater than 0.3 ppm.

Levels of fluoride requiring adjustment or withholding of supplement dosage were found in varied regions of the state, not just in the known belt of natural fluoride that runs through eastern North Carolina, South Carolina, and Virginia. Thus, it is necessary to sample the water supply before prescribing a fluoride supplement — unless the provider has *specific prior knowledge* of the fluoride content of the patient's water.

Determination of Appropriate Dosage

After determining the fluoride levels of a patient's multiple sources of water (either by submitting samples or obtaining information from water companies, schools, Dental Health Section, etc.), the physician must determine the supplement dose to prescribe. This is done after estimating the percentage of daily water intake from each source and consulting table 3. For instance, if a 3-year-old child consumes well water at home with <0.1 ppm fluoride, but goes to day school in down where the water is fluoridated at 1 ppm fluoride, one must estimate the water consumption from each source. If it appears that the child consumes about half his water from each source, the net result would be the same as if the child were drinking water containing 0.5 ppm. One should then refer to table 3 to determine the correct dose (0.5 mg/day). A variety of similar circumstances can occur.

It is essential to determine whether an infant is being exclusively breast-fed, bottle-fed, or obtaining nutrition from both sources. Breast-fed babies should be supplemented fully, since there are very low amounts of fluoride found in human milk, even when the mother resides in a fluoridated area.[31] The major manufacturers of infant formulas have removed fluoride from their products which previously contained variable levels. An infant on formula now receives fluoride almost exclusively from the water that is mixed with the formula. The physician must determine the proportion of bottle-feeding and reduce the supplement accordingly for those infants receiving nutrition from both sources.

For purposes of fluoride intake calculations, an adult is assumed to consume daily an average of one liter of water. If the water is fluoridated at 1.0 ppm, then 1 mg of fluoride is consumed. An infant, then, according to table 3, should have a daily intake of about 0.25 liters of fluoridated water, or 0.25 mg of fluoride. The determination of fluoride intake can be difficult. The total amount of water consumed daily must be determined, whether it is in the water, in juice made from concentrate, formula from a concentrated powder or liquid, or in other forms. It should be recommended that parents try to standardize the amount of water consumed by the infant, as well as the type of formula (i.e., powder, concentrated liquid, etc.).

Since excessive fluoride can cause fluorosis, parents should contact the physician when changes occur in the infant's consumption of liquids so the fluoride supplementation can be adjusted. In a fluoridated community, a 1-year-old child drinking four 8-ounce bottles of formula daily would receive 1 mg of fluoride (four times the optimal) if concentrated powder were used, and 0.5 mg of fluoride (twice the optimal) if concentrated liquid (diluted 1 : 1 with water) were used. Using "ready to use" formula would mean that no fluoride is consumed via the formula, and the water or the supplement used should provide the infant's needed fluoride in the recommended amount. The practitioner must have a thorough understanding of the patient's total flouride exposure. Since most young children do not see a dentist before age 3 or 4, the complexities of controlling fluoride dosage for infants are largely the responsibility of physicians.

Fluoride tablets are now available in 0.25, 0.5 and 1.0 mg fluoride formulations. There are several commercial brands available.[3] Additionally, many pharmacies can provide a generic product. The tablet should be chewed before swallowing to provide topical benefit. Fluoride drops, providing 0.125 mg of fluoride per drop, should be used for those who cannot chew a tablet. No more than 264 mg NaF, or 120 mg fluoride, should be prescribed at one time for safety reasons.[3] The product should be kept in a "child-proof" container in a secure place. The biggest difficulty with fluoride supplements is patient compliance.[12-15, 32] The physician must routinely encourage and attempt to monitor the child's supplement use.

Conclusion

It is hoped that this article will encourage and assist physicians in North Carolina in providing the appropriate dosage of fluoride supplements to those children in need. The medical profession must work closely with dentists and other health professionals if systemic fluorides are to be used to greatest benefit in our population.

Summary[22]

1. All children should receive some form of systemic fluoride and appropriate forms of topical fluoride.
2. If a child is not receiving optimal home (1 ppm) or school (4.5 ppm) water fluoridation, then the physician should consider prescribing systemic sodium fluoride supplements (tablets or drops).
3. The correct dose must be determined based on patient age and fluoride content of the patient's multiple water sources.
4. Special attention is necessary concerning fluoride intake for children breast-feeding or consuming infant formula.
5. To arrive at the correct fluoride dose, these steps should be followed:
   - A. *Always* have a sample of the home water supply analyzed for the fluoride content before prescribing a fluoride supplement. If the child drinks significant amounts of water from more than one source of unknown fluoride content, the other sources should be analyzed as well. The State Laboratory of Public Health will provide sample bottles, 919/733-7308.
   - B. When the fluoride content of the water has been determined, the value and the child's age should be matched on table 3 to arrive at the correct supplement dose.
   - C. If the child is drinking water from more than one source that contain various amounts of fluoride, one must estimate the percentage of the daily water intake from each source and adjust the dose accordingly. It is important to **thoroughly understand** the child's systemic fluoride exposure and to use sound judgment in calculating the dose.
   - D. Over 130 schools in North Carolina have school fluoridators which fluoridate the water at 4.5 ppm. **Children who attend such schools should not receive a systemic supplement, even though their home water contains no fluoride.** Information on the schools in your area that have school fluoridators can be obtained from the county health department or the Dental Health Section in Raleigh at 919/733-3853.
6. The Dental Health Section can provide lists of communities and schools in North Carolina that are optimally fluoridated.

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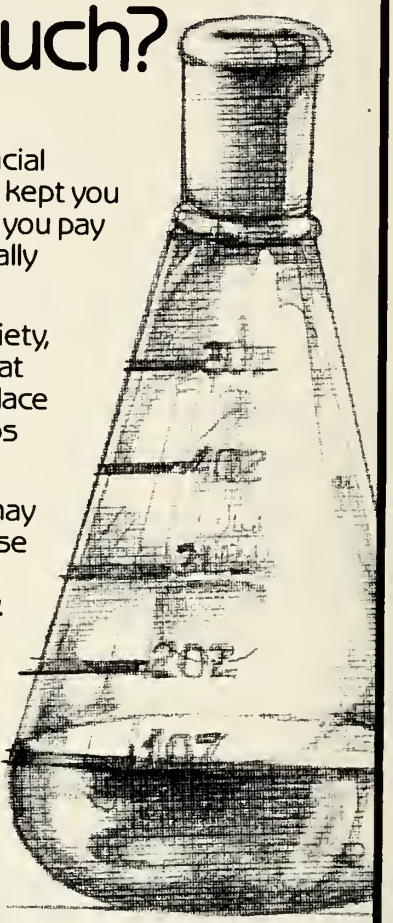

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SCIENTIFIC ARTICLE

Successful Therapy of Postherpetic Neuralgia of the Trigeminal Nerve

Stanley Grosshandler, M.D. and Wayne Gray, LPT

- *The care and treatment of a middle-aged woman with trigeminal nerve pain.*

THIS is the story of the successful treatment of a patient with chronic pain caused by postherpetic neuralgia of the fifth cranial nerve.

Irritation of the trigeminal nerve is not only amongst the worst afflictions known to man; it is also one of the most refractory to treatment. Characterized by recurrent paroxysms of pain described as either stabbing or burning, the duration may vary from a few minutes to several hours with variable frequencies of attacks. The patient lives in constant fear of recurring pain.

The etiology of this problem includes trauma, neoplasms, aneurysms, meningeal infection, herpes virus, and trigeminal neuralgia (tic douloureux).[1] There is evidence that the excitatory state necessary to fire a pain attack may be built up over a considerable period of time by a temporal summation of afferent impulses. This results in a state of self-maintenance of excitation in the brain stem and spinal nucleus of the trigeminal nerve. This may explain the suddenness, intensity, and brevity of attacks.[2]

The patient is a 57-year-old white female college professor who in the fall of 1979 noticed a painful blister formation on the inside of her mouth and under the left eye. A diagnosis of herpes zoster was made and steroid treatment, both oral and parenteral, was begun. The blister formation soon disappeared; however, it was followed by pruritis and lid lag of the lower lid of her left eye. The lid lag permitted the eyelash to contact the cornea causing an abrasion. She also experienced burning along the maxillary division of the trigeminal nerve.

A diagnosis of neurotropic lid function with secondary corneal scarring and spastic entropion of the lower lid was made and conservative treatment elected. This consisted of a combination of blephamide ointment, dexamethasone ointment (Decadron), and hydroxypropyl cellulose (Lacriset). Although there was some diminution of her discomfort, it was decided 20 months later to perform a resection of the muscle of the lower lid. The surgery obtained considerable improvement of symptoms and with the aid of her previous medications she has been able to keep the corneal problem under control.

In an attempt to obtain relief from the burning sensation in her face she consulted several medical practitioners and a variety of medications were tried. This included steroids which caused her to gain 40 pounds: amitriptyline, carbamazepine (Tegretal), phenytoin (Dilantin), haloperidol (Haldol), propoxyphene compounds (Darvon Compounds), hydroxyzine (Atarax), diphenhydramine (Benadryl), baclofen (Lioresal), and meclofenamine (Mecolmen). None proved to be efficacious.

In September 1983 the patient was seen with the chief complaint of constant burning on the left side of her face under the left eye. The pain was sharp, felt like an electric shock, and was made worse by cold water or cool air. Her scalp was occasionally sensitive. The ocular pruritis remained but was controlled by the medications previously mentioned. She was taking no medication for the pain.

She had continued to teach and stated, "It is often difficult to teach six classes when my face hurts." She did notice the pain was increased by stress; and also experienced difficulty in sleeping, lack of energy, and spells of depression and crying. A Zung index was 33. The only positive physical finding was decreased sensation over the distribution of the second branch of the fifth cranial nerve.

It was felt that this patient had postherpetic neuralgia of the maxillary branch of the trigeminal nerve, and therapy was initiated with diflunisal (Dolobid) 500 mg with breakfast and supper, doxepin 50 mg HS, and valproic acid 250 mg with each meal. The valproic acid (Depakane) was given with food, as was the diflunisal to minimize gastric irritation. When the enteric coated preparation Depakote became available the patient was placed on it. Sleep, energy and depression improved.

Physical therapy commenced employing biofeedback, ultrasound, and medical galvanism,[3] with the galvanism proving to be the most effective modality.

The patient was taught by home tapes and EMG biofeedback to relax. Prior to each PT session she spent several minutes relaxing. The galvanic apparatus was attached to her face, taking several precautions to prevent skin burn, and the current was gradually increased. She started at 2 milliamps for a very brief period of time; however, she was eventually able to tolerate 17 milliamps over a 25-minute period. She had a total of 12 sessions.

Within a week the patient reported decreased pain with improved sleep and decreased depression. Following a month of treatment she reported as many as six pain-free

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days at a time. Due to package insert warnings for valproic acid, the patient on two occasions had valproic and doxepin levels determined plus PPT, Protime, LDH, SGOT, and SGPT. All were at desired levels.

Five months from her initial visit the patient was seen with plans to reduce her medications. During the course of the visit she remarked that she had experienced some abdominal distress the past several days. An examination of the abdomen was suspicious of an abdominal catastrophe and surgical consultation was immediately obtained. A diagnosis of ruptured diverticula was made and a colon resection was performed, resulting in a 17-day hospitalization. The patient made an excellent recovery.

The patient was not seen for three months during which period she had discontinued her medications as a result of her surgery. The facial pain had returned but not to the same degree as previously. The medication routine was restarted and she had immediate pain relief. Within a two-month period both doxepin and valproic acid had been discontinued with only occasional use of the diflunisal.

This lady represents the typical postherpetic neuralgia patient. In an effort to obtain pain relief she had consulted many physicians, receiving multiple prescriptions. She was indeed fortunate she had not become an iatrogenic drug abuser.

She manifested many signs of the chronic pain patient, including a reactive depression. This is found in as high as 80-90% of chronic pain problems.[4] Though her Zung index was only 33, the symptoms of sleep difficulty, loss of energy, admission of feeling depressed and crying clearly indicated she would benefit from a tricyclic antidepressant (TCA).

Amitriptyline and doxepin are the TCAs of choice in chronic pain,[5] with doxepin appearing to have the lesser incidence of side effects. It is postulated that the antidepressant blocks the reuptake of serotonin by the nerve endings and thus increases the concentration of serotonin at the receptor sites. This is clinically manifested by improved sleep, improved energy, decreased depression, and decreased awareness of pain.

A nonsteroidal anti-inflammatory (NSAID) was chosen for its non-addicting analgesic effect plus antiprostaglandin synthesis action.[6] The NSAID chosen has a twice-a-day dosage, making for better compliance, and it appears to have the least gastric irritation of commonly used NSAIDs. The patient was also advised to take the medication with food.

The anticonvulsants phenytoin and carbamizide have long been efficacious in the treatment of trigeminal neuralgia; however, in this case they had not been helpful, and therefore valproic acid was used.[7] The mechanism of action of this class of drugs in this problem is stated to be a reduction of post-tetanic synaptic transmission within the spinal cord, reducing the perceived sensation of pain.[2]

Of significant importance in the therapeutic success of this patient is her basic personality structure. A well-educated person, harboring no desire of secondary gain, her intense determination to defeat her medical problem and continue with her career played a major factor in her treatment.

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Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

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1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

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CALCIUM CHANNEL BLOCKER**

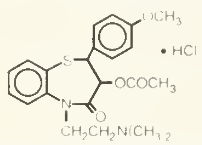
Please see full prescribing information on following page. 2/84

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis- The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm. CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20% In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3% asthenia (1.2%), AV block (1.1%). In addition, the following event were reported infrequently (less than 1%) with the order of presenta tion corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradyca dia, palpitations, congestive heart failur syncope.
Nervous System:	Paresthesia, nervousness, somnolenc tremor, insomnia, hallucinations, and amnesi
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomitin mild elevations of alkaline phosphatase, SGO SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivit
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes c vasospastic angina developed periods of transient asymptomati asystole approximately five hours after receiving a single 60-m dose of CARDIZEM.

The following postmarketing events have been reported infre quently in patients receiving CARDIZEM: erythema multiforme; leu kopenia; and extreme elevations of alkaline phosphatase, SGO SGPT, LDH, and CPK. However, a definitive cause and effect betwee these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limite Single oral doses of 300 mg of CARDIZEM have been well tolerate by healthy volunteers. In the event of overdosage or exaggerate response, appropriate supportive measures should be employed i addition to gastric lavage. The following measures may be considere

Bradycardia	Administer atropine (0.60 to 1.0 mg) If ther is no response to vagal blockade, administe isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high degree AV block should be treated with ca diac pacing.
Cardiac Failure	Administer inotropic agents (isoprotereno dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenc bitartrate).

Actual treatment and dosage should depend on the severity of th clinical situation and the judgment and experience of the treatin physician

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/k and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s i these species were 60 and 38 mg/kg, respectively. The oral LD_{50} i dogs is considered to be in excess of 50 mg/kg, while lethality wa seen in monkeys at 360 mg/kg. The toxic dose in man is not know but blood levels in excess of 800 ng/ml have not been associate with toxicity

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coro nary Artery Disease or Angina Pectoris at Rest Due to Coro nary Artery Spasm. Dosage must be adjusted to each patient' needs. Starting with 30 mg four times daily, before meals and a bedtime, dosage should be increased gradually (given in divide doses three or four times daily) at one- to two-day intervals unti optimum response is obtained. Although individual patients ma respond to any dosage level, the average optimum dosage rang appears to be 180 to 240 mg/day There are no available data concer ing dosage requirements in patients with impaired renal or hepati function. If the drug must be used in such patients, titration should b carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acut anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CARDIZEM may be safel coadministered with short- and long-acting nitrates, but ther have been no controlled studies to evaluate the antiangina effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (ND 0088-1771-47) and in Unit Dose Identification Paks of 100 (ND 0088-1771-49). Each green tablet is engraved with MARION on on side and 1771 engraved on the other. CARDIZEM 60-mg score tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Uni Dose Identification Paks of 100 (NDC 0088-1772-49). Each yello tablet is engraved with MARION on one side and 1772 on the othe

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SPECIAL ARTICLE

How Can We Know When We Are Doing More Good Than Harm For A Terminally-ill Cancer Patient?

Robert H. Fletcher, M.D.

- *The suffering of terminally-ill cancer patients cannot be relieved if the physician is working with inaccurate information.*

THIS paper is about our attempts to relieve patients' suffering when death is inevitable and relatively imminent. An example of that situation is the care of terminally ill cancer patients.

My thesis is that sometimes we make inappropriate decisions toward our goal of relieving suffering in part because we are working with inaccurate information. Our eyes, ears, hands and minds have failed to provide us with an accurate view of the world as our patients see it. If this occurs, we (and more to the point, our patients) are doomed to failure even before we begin to make what might be regarded as clinical or ethical decisions.

The subject, then, is bias (a systematic error) in our perception of our patients, and its consequences. I will illustrate the failures attendant upon biased observation by anecdotes and by more formal science, original research.

Relieving Suffering and Preventing Untimely Death

First, let us consider our objectives for patients. I was taught as a medical student that our role as physicians is to relieve suffering and prevent untimely death. But not uncommonly one must choose between the two in an individual patient; that is, one might relieve suffering *or* prevent untimely death. For example, one might engage in tests and treatments which are extremely uncomfortable in the short run in order to cure a fatal disease in the long run.

There is, obviously, a period of transition between the time when we hope to prevent untimely death — to cure the patient — and the time when relief of suffering is all that is available to us. The various people involved — patient, doctor, nurses, family — have to lose much of their faith in cure, and come to put more value in caring alone. In actual practice, the period of ambiguity in management sometimes extends well beyond the point when relief of suffering is the only reasonable goal, were we to step back and look at the situation.

Sometimes, therefore, our actions result in *neither* relief of suffering nor prevention of death. We find ourselves ordering uncomfortable diagnostic tests and treatments out of wishful thinking with little chance of cure, because we have not made the painful decision that cure is no longer a reasonable objective. After all, there comes a time when death is no longer considered untimely, all things considered.

Relieve Suffering

What is the relief of suffering in a terminally-ill cancer patient? Physicians who have studied this suffering carefully, talking candidly with patients and those close to them, name four main components: pain, dyspnea, nausea and loneliness.

Pain is common in cancer. Probably pain is what patients fear the most about the disease. We have the medications to relieve even the most severe pain. But study upon study has shown that actual doctors, taking care of actual patients, often prescribe medication well below the doses necessary to relieve pain. Students of pain advise one thing — with substantial consensus — and we do another.

There are many reasons why we do not relieve pain properly. We are concerned that our patient not become addicted (in the few remaining days of life, mind you!). Perhaps we are skeptical about the severity of the pain. Sometimes we are making legitimate efforts to avoid pharmacologic risks with high doses of narcotics. Whatever the reasons, it seems that relief of pain is often not done well in our hands — relative to what we *could* do.

Dyspnea is apparently an awful feeling. In managing it, we should bear in mind that the perception of dyspnea mainly originates from activated stretch receptors in the chest — stiff lungs. Dyspnea is not what one feels because he or she is hypoxemic (although patients with dyspnea are often hypoxemic as well).

To relieve dyspnea, giving oxygen is not directly helpful, although it may be an effective placebo. Rather, dyspnea should be managed more directly, if possible, by attacking the anatomic problem in the chest — by thoracentesis, local radiotherapy and the like. Failing that, the mind-altering effects of narcotics provide relief.

Nausea is so often the result of chemotherapy. Do we give enough weight to its effects when we give palliative chemotherapy — that is, when relief of suffering is the main reason why the chemotherapy is being given?

Loneliness is the fourth form of suffering. We often put emotional distance between us and the dying. It is quite

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natural to want to do so. One way we maintain this distance is to use the technical aspects of care as a device to avoid the real issues candidly. For example, we may spend what little time we have for our patient discussing laboratory tests and their results, or the technical aspects of treatment, rather than prognosis and feelings.

Unfortunately, the published medical literature usually does not provide the information we need to make humane decisions regarding pain, dyspnea, nausea and loneliness. Success and failure are usually described in terms of tumor-mass and survival, as if these were the only concerns. The state of the tumor is related to the state of the patient, of course. But the relationship is by no means very precise. The tumor may be regressing, while the patient is suffering or dying.

Seeing What Our Patients See

Suppose that we have made a clear decision that relief of suffering is all we are attempting to do. And we want to see what does and does not promote that. It would be naive to assume that we can simply clear our head and make accurate observations, as any fair-minded person could.

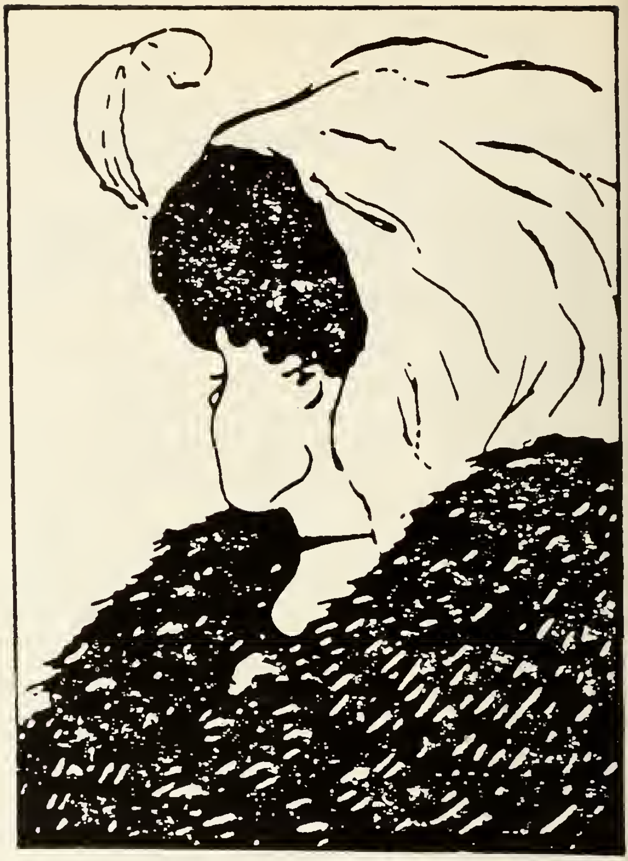
In general we do not — cannot — make observations altogether free of our own ideas about what should be seen. Epistemologists, philosophers of science who deal with the origin, nature and limits of knowledge, call this the ''theory dependence of observation.'' Our observations are colored by the theories we subscribe to before we make the observations. As one scholar put it, ''it often happens that when different disciplines look at the same thing (the same lines on the paper, for example), they *observe* different things.''[1]

Figure 1 illustrates this problem. Some see in it a young woman, some an old woman. Both are correct.

To quote a scholar of this problem:

> ''Note . . . how the cognitive orientation seems to give meaning to the lines or parts of the drawing rather than the other way around. Imagine what it would be like to be part of an interdisciplinary group [for example, a conference of patients, family, consultants, nurses and social workers] discussing a problem in which the young-old woman, or something analogous [e.g., importance of various symptoms, preference for treatment] played a part. What would happen if your discipline allowed you to see the young woman, while the other disciplines interpreted it as an old woman and you didn't recognize the difference? Would you be tempted to retreat to your own narrow discipline and categorize these other folks as just silly?''[1]

Our care of the terminally-ill cancer patient does involve many ''disciplines'': patient, family, physicians, nurses, social workers, and more. Each has his or her own perspective. Therefore we should be humble in our ability to see what is ''really'' there, and try extra hard to see things as the patient does and also as others involved in the patient's care do. The gap between you, patient, family, nurse and others may be wider than you think. As a result, you might be misled in assembling what you consider ''the facts'' for a management decision.



Death

How much suffering does death itself — the immediate process of dying — involve? To the living and healthy, the act of death seems distinctly unpleasant. It can sometimes appear grotesque in the final seconds — gasping respirations, seizures, and the like. But from everything we know, these occur after the patient is unconscious. What about the seconds leading up to death?

A vivid description of the moments before death is provided by David Livingstone, the British explorer. He wrote about a time when, for all intents and purposes, he was dying — in a violent, gruesome way, for that matter. He describes being attacked by a lion:

> ''I heard a shout. Starting and looking half round, I saw the lion just in the act of springing upon me. I was on a little height; he caught my shoulder as he sprang and we both came to the ground below together. Growling horribly close to my ear, he shook me as a terrier does a rat. The shock produced a stupor similar to that which seems to be felt by a mouse after the first shake of a cat. It caused a sort of dreaminess in which there was no sense of pain nor feeling of terror, though quite conscious of all that was happening. It was like what patients partially under the influence of chloroform describe, who see all the operation but feel not the knife. This singular condition was not the result of any mental process. The shake annihiliated fear, and allowed no sense of horror in looking round at the beast. The peculiar state is probably produced in all animals killed by carnivora; and if so, is a

merciful provision by our benevolent Creator for lessening the pain of death."[2]

Where is the anguish, the fear and pain? Conspicuously absent.

This anecdote is backed up by more systematic studies of patients successfully resuscitated in hospitals. When asked to look back on their "deaths," their thoughts were contemplative, detached, even serene. Some expressed frustration at being brought back from the edge of death by cardiopulmonary resuscitation.

Thus, as best we can tell the immediate act of dying is not so arduous. In itself, it does not appear to be part of the suffering. We even know something about the mechanism for this. There appears to be a release of neurotransmitters, morphine-like substances and others, that change the mind set. Hence the title of the article about Livingstone: "Endorphins I Presume?"

The Decision Whether to Resuscitate

Now let us examine the decision to resuscitate. Here, in viewing the quality of our terminal care we need not evoke anything so subtle as the theory dependence of observation. Apparently we — or at least physicians like us — do not seek patients' opinions or guess what they want at all well. I will illustrate this with a study conducted at Harvard teaching hospitals in Boston, recently published in the *New England Journal of Medicine* (table 1).[3] The authors studied the decision-making process surrounding the care of 154 patients who were resuscitated in the hospital. The responsible physicians consulted patients' families about possible resuscitation only a third of the time; patients themselves were consulted less often. About a third of patients who survived resuscitation stated that they did not want it then, and would not want it in the future.

In the situation where cardiopulmonary arrest is anticipated some accurate information, for the purpose of relieving suffering, could apparently be obtained by simply asking the patient.

Terminal Care

How can we provide terminal care better in the days and hours before death? One view of it is provided by a study done in a community hospital in Washington state.[4] The terminal care of 30 patients, who died expectedly with cancer, was reviewed (table 2). Suffering was usually not relieved, but, more importantly, procedures were often performed that were unnecessary and increased suffering.

On a practical and constructive note, the investigator made the following suggestion: "The frequent occurrence, the quick onset, and the unpredictable timing of these problems suggest that physicians should write 'conditional orders' to relieve the symptoms, similar to CCU protocols."

Table 1
The Decision to Resuscitate in a University Teaching Hospital (154 Patients)[3]

	Percent of Patients
Physician formed prior opinion	68
Family consulted	33
Patients discussed with physician	19

Table 2
Terminal Care in a Community Hospital (30 Patients)

	Percent of Patients
Failure to relieve	
Pain	92
Nausea/vomiting	91
Dyspnea	100
Pulmonary secretions	93
Routine, slightly noxious unnecessary procedures	
Restraints	27
Suction	27
Frequent turning despite pain	43

Nutrition

The decision whether to provide nutrition to the dying patient is difficult to make on its own merits. The decision is tied up in a deeply-held belief that providing food and water is basic, humane care. Giving nutrition is emotionally compelling. But does it always do more good than harm, toward the goal of relieving suffering in an individual patient? This question was addressed in a recently published article entitled "Guiding the Hand that Feeds."[5]

The authors observe that "family members and health professionals sometimes project their own feelings onto the patient. . . . Judgments about the quality of life are best based on direct observation of the individual patient rather than on generalizations." The authors point out that although feeding is considered "ordinary," not "extraordinary," care, "all medical treatments, including tube feedings and the use of respirators [an example of "extraordinary" care], provide both benefits and burdens. The crucial issue is not the nature of the procedure but whether the benefits of a treatment outweigh the burdens for a particular patient. We suggest that in some cases the burdens of feeding may outweigh the benefits. Instead of being humane care, tube feedings may be painful, invasive, and impersonal for some patients."

The implications go beyond tube feeding to the common practice of urging food and water on patients who refuse them. Just how thirsty can a person be if he or she is alert and able to communicate, can swallow, is offered liquid, and refuses? How hungry can that person be if he or she refuses food, even their favorite foods, offered by a loved one? For many of us, the answer bears re-thinking. Sometimes we may add to the suffering of terminally-ill cancer patients by nagging them about food and drink.

Placebo Effect

The placebo effect is the relief of suffering by a means — for example, saline injections or sugar pills — for which the specific mechanism is not known. It is an old ally. But we consistently underweigh its value, and thereby forego a powerful tool in our armamentarium.

A simple expression of interest and concern, being in control and holding appropriate optimism, can relieve physical suffering. I was reminded of this by a recent encounter. I went to visit a young woman with terminal cancer who had been hospitalized with yet another setback. I wondered, as I often do, what I could offer that would really be helpful. It seemed our conversation would be awkward, painful. But mother and daughter were pleased to see me. They recounted the events of the recent days; the patient described how she felt now. I just listened and asked a few simple questions, that was all. If any skill was involved, it was simply going in there and not being too ill-at-ease. And it seemed as if I *did* have something to offer! They were happier when I left — although there was no new diagnosis, and no better plan for treatment.

What can be learned — relearned — from this incident? The physician's presence is effective, in and of itself. There is a large, strong scientific literature to back this up, for those of you who doubt my experience, or your own. The placebo effect can be used to enormous effect to relieve suffering in dying cancer patients — at least, that's what the evidence suggest. Why doubt it?

Other Determinants of Clinical Decisions

Now what, more specifically, are these gremlins that interfere with our powers of observation, and hence the care of our patients? You are familiar with them. There are a great many. They distract us. They increase noise relative to signal, like static on a radio.

These gremlins are all the sorts of things that affect the practice of medicine, other than biology and caring. The following is an incomplete list and the entries are not mutually exclusive.

Time. Physicians are genuinely busy people. When we are with any one patient we are aware that others need us and could benefit from our efforts too. Only someone altogether unfamiliar with clinical medicine or otherwise unrealistic could regard the solution as "just try harder." So as a minimum, I would only suggest that we do what is simple, direct, and costs little *net* time. But we should not forget that many of the things we currently do, or ask to be done, are not useful and also take time. Some examples include arranging and tracking down the results of diagnostic tests when the need to know is small, and administering chemotherapy properly but for the wrong reasons.

Need for action. We are a society that is very uncomfortable with errors of omission — doing less than could have been done when things are going badly. On the other hand, we are quite tolerant of errors of commission — trying, even if things do not work out well. We want action. So we end up doing things for people, in the words of T. S. Eliot,

> Not for the good that it will do
> But that nothing may be left undone
> On the margin of the impossible.[6]

Sometimes we end up doing harm in this way. To the extent that we can extricate ourselves from the social values surrounding us, it is sometimes worth it for our patients.

Law. Of course malpractice law in this country reinforces this habit.

Money. The exchange of money also adds to our problem. Most medical care in this country is fee-for-service; we are paid more for doing more. Fortunately, medical care is still glued together strongly by sincerity and respect, decency and human values — on the part of doctors, patients, hospital administrators, and the rest. Imagine what it would be like if we all pursued our self-interest without restraint? But fee-for-service payment cannot help but have some effect on medical decisions.

One solution that has been proposed is prepayment. This method of reimbursement is growing in prevalence, and puts the economic incentive on doing less. What will be the effect on the care of terminally-ill cancer patients? While doing less sounds on the face of it like it would be bad for patients, prepayment could be an opportunity for good or harm depending on how we behave. Think back to the study of terminal care — how often patients in pain were bothered by turning and suctioning prior to death. How about high technology — CAT scans, etc. — in the last few days of life? Doing less of some of the things we do can be better.

There are other forces: religion, culture, guilt and the personalities of the individuals involved. All of these and more determine human values, and thereby our actions as physicians.

My message, then, runs as follows:

1) If the objective of care of the terminally ill cancer patient is to relieve suffering, and we are working with inaccurate information, inappropriate clinical (or ethical) decisions will follow. So we must try very hard to begin with sound information.

2) It is difficult to get accurate information — that is, from the patient's point of view — because "when different people look at the same thing . . . they *observe* different things." We must observe on our own, to be sure, but be humble and skeptical in our powers of observation. To improve our observations, we must reproduce the rigor of the scientific method, in a small way, each time we gather important facts.

3) There is ample evidence that we often do act on inaccurate information in the care of terminally ill cancer patients. My illustrations point to some of the misconceptions we, or physicians like us, commonly have and how they might be avoided.

4) A great many forces other than biology — money, law, culture — determine clinical decisions. Sometimes they act in a perverse way; they can be a substantial distraction in the pursuit of our goals, to relieve suffering in human terms.

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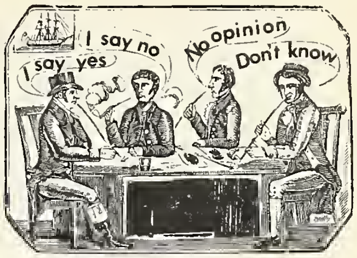
PHYSICIANS' FORUM

Responding to Patients Who Refuse Life Saving Treatment



Eugene W. Linfors, M.D., editor

The question for February is: **How should physicians respond to patients who refuse life saving treatment (e.g., blood transfusions)?**

From Dr. Allen R. Dyer, a psychiatrist in Durham.

No physician has a right to treat any patient without the patient's informed consent. Legally this is governed by the laws of battery. A physician who treats without consent is committing an assault. Practically, one assumes consent when a patient comes asking for help and agreeing with what is proffered, but there are a number of situations where a patient may refuse treatment. This is their legally guaranteed right which should be respected by the physician, not only because it is legally required, but also because it is morally required.

The moral requirement is argued by philosophers as based on the principle of autonomy and self-determination. Any person, it is held, has a right to determine what happens to them because they are autonomous. Much has been written, especially in the past two decades, about the requirement of informed consent, which is designed to protect the patient's autonomy. The issue of informed consent, first developed in relationship to surgical procedures in the early twentieth century, received much attention during and after the Nuremburg trials because of involuntary experiments conducted by Nazi physicians. Recently the consumer movement has given impetus to such concerns with increasing objections to the ''Doctor-Knows-Best'' kind of paternalism.

There is a philosophical problem in arguing for informed consent on the grounds of patients' autonomy. What does it mean to be autonomous? If it means to be completely independent, few people meet that criterion. Actually consent must be (1) informed, (2) voluntary, and (3) competent (according to DHHS regulations), and so there is much room for interpretation. Nonautonomous persons, e.g., children, the senile, the comatose, and some psychiatric patients, deserve special consideration.

The matter becomes of practical importance when a patient refuses a treatment the doctor considers essential. The patient may seem irrational, even crazy. Such patients are especially frustrating to doctors whose personalities require them to be in control or who have difficulty having their judgment questioned.

A classic example of refusal of treatment is the Jehovah's Witness' refusal of blood transfusions (but not other medical or even surgical treatments). This refusal is based on religious grounds, an interpretation of a Biblical prohibition of the ''eating'' or consuming of a creature's life: ''Only be sure that thou eat not the blood: for the blood is the life; and thou mayest not eat the life with the flesh'' (Deuteronomy 12:23). While it may seem irrational to many physicians, Jehovah's Witnesses regard it as an article of faith and a particular test of one's adherence to God's Law. Thus it may be easier for a physician or surgeon to empathize with a Jehovah's Witness' refusal of blood if one appreciates the patients' belief system. The risk of death may not seem so bad compared with an eternity of damnation.

Practically, the matter may not be as simple as letting the patient decide for himself. The doctor may be forced into attempting surgery without the possibility of blood transfusion. The doctor may be tempted to insist on conditions that would make his own task easier. The doctor may be tempted to refuse to treat the patient if the patient does not comply with the doctor's wishes. Obviously such conditions do strain the physician, but most would probably try to respect the patient's wishes and do what is possible under the circumstances.

Somehow these situations often turn into heated confrontations, challenges to the physician's authority, control struggles. At another level the patient may be more concerned with pressure from other church members and might actually welcome alternatives such as certain blood products or plasma expanders.

The issue of children is a special case. Children are not considered to have the right of refusal (or assent) since they are not autonomous and have not reached the age of reason. Hence parents must consent for them, and if the parents do not consent to a treatment that the physician deems necessary, the physician may seek a court order. This is actually fairly routine even in middle-of-the-night situations.

Another group of patients that is not considered autonomous (competent) are those with mental disorders. The question of the legal rights of committed psychiatric patients to refuse psychotropic medication is a complicated one, which is not settled legally. It can become a practical question for the physician with a patient who has become depressed and who may prefer to die (or profess to) rather than continue with treatment. This is not uncommon with renal dialysis patients, cancer patients and others. It gives rise to the ''Whose Life Is It Anyway?'' debates popularized in the play and movie by that name. Such patients do have the right to refuse treatment, but they should not be allowed to exercise that right without the benefit of psychiatric consultation. It is possible that their depression can be treated, and that they would feel different about the decision were they not depressed. Often with such patients part of their depression provokes rejection in those who are caring for them, who may feel that their efforts to help aren't appreciated and feel tempted to let them have their own way out of frustration. Here, as in so many cases in medicine, the psychiatrist's concept of "therapeutic alliance" becomes extremely important. The doctor must have the patient's trust for any treatment to be successful. Without such an alliance, even the best treatment plan may be subverted either actively or passively through noncompliance.

Patients have both a legal and a moral right to refuse treatment, which the doctor has an obligation to respect. But the doctor also has an obligation to try to help the patient in whatever way possible, and this may mean not rejecting the patient who rejects us, but seeking with the patient alternatives that may be acceptable to both.

From Dr. H. J. Proctor, a surgeon in Chapel Hill.

I believe that individuals who are of legal age and mentally competent should have the freedom to control their own therapy. Even more specifically, with regard to individuals such as Jehovah's Witnesses who refuse blood transfusions, I believe that physicians should honor the religious beliefs of their patients. Consequently, I have no qualms about caring for Jehovah's Witness patients, and I will not transfuse blood products against their wishes, even if this means the death of the patient. In point of fact, this is rarely the situation since it is an unusual Jehovah's Witness patient whose hemoglobin levels sink to the point below which they cannot compensate by increased extraction and increases in cardiac output. As far as mentally incompetent patients or legal minors are concerned, I do not feel that another individual's beliefs should be inflicted upon them and accordingly if I felt that a blood transfusion was in the best interest of the patient I would proceed to get court authorization to treat the patient in what I felt was the most appropriate manner. Lastly, as a physician, the responsibilities I feel toward my patients are medical, ethical, social, religious, and legal in scope, and I would defend the right of any physician, once a contractual arrangement has been made with a patient, to do whatever he or she feels is appropriate.

From Dr. Harold R. Silberman, an emergency medicine physician in Durham.

No single event in the doctor-patient relationship polarizes each into a power struggle more than a Jehovah's Witness refusing blood products during a serious medical or surgical illness. That apparent loss of cooperation between the two individuals, with its attendant rigid overtones, based on the one hand upon religious beliefs and on the other hand upon medical conviction, often infuriates the physician. At the other end of the spectrum of refusal of therapy are those individuals whose addiction and/or lack of will power interfere with following instructions. And, after all, instructions to abstain are often more important than many things we prescribe in a bottle or syringe, and many bad habits are self destructive.

Between these two extremes is a range of noncompliance that includes: not filling prescriptions; taking less of the drug than prescribed; not keeping appointments; refusing to follow instructions about self monitoring (as in diabetes); and taking medications (usually over-the-counter) specifically proscribed by the doctor. Because this type of behavior goes on over many years it doesn't carry the stigma of a sudden decision to refuse a critical treatment.

Younger but sometimes even older physicians also become irate and thereby less effective when a portion of the physical examination is declined or a proposed test, such as an LP, is declined.

But there can be another, somewhat more subtle area of disagreement or conflict. It occurs when the patient is advised to undergo a procedure or therapy that is not temporally critical, *may* not be life saving, carries some risk of significant side effects, and is projected to be demanding in time and cost. Such a situation can develop in many settings but perhaps more frequently when dealing with cancer. Therefore, while advising post graduate fellows who are training in oncology, it's been my habit to teach the principle that *not every* patient is capable of participating in an aggressive cancer research protocol, even when it's explained that such, though novel, represents the *best patient care* of the day. For example, how many individuals with acute non-lymphocytic leukemia can understand, much less handle, the concept of a bone marrow transplant that carries some risk of immediate death, without ever returning home; a significant expectation of serious continuous side effects for a large fraction of patients who survive the transplant; and less than a 40% chance of permanent cure for anyone?

When dealing with more sophisticated and braver patients, it's not unreasonable to ask: "How much of your personal resources do *you* want to expend battling this illness?" Because Americans put such a high premium on saving/sustaining life, it sometimes stuns the physician when a patient decides against doing so.

Once we accept the fact that patients may and do go against our best advice, there are five critically important things to remember when negotiating in a setting where someone is refusing life-saving treatment. First, confrontations or power struggles are usually "no-win" situations for all concerned. Second, even when seriously ill, the adult needs to be treated like an adult, not like a child — we are not everyone's father nor are we God. Third, there is a real difference between a patient being incompetent and showing poor judgment. Incompetent folks may and often should be placed under someone's jurisdiction whereas people who make what we label poor decisions can neither be restrained or incarcerated. No where else in the medical system than an emergency room does this concept require more understanding. An angry, demanding, impatient, wounded or hurting adult may elect to sign out AMA (against medical advice) whereas if inebriated, that same person should be restrained, studied and appropriately treated when it's a life-saving emergency. Fourth, managing the so-called difficult patient can be a significant psychological stress to the vulnerable physician. In this regard, its been comforting to rationalize that if one is mostly consumed by a single interaction, there's little left for the patients that follow. Fifth, all of us need to gain more humility by remembering clinical vignettes. There are heroin addicts who have left hospital short of completing the prescribed course of antibiotics for SBE and yet are cured. Pancytopenic patients have declined hospitalization to stay home because a child is coming for a visit and yet they didn't hemorrhage to death or become septic.

The care of the physician troubled by such refusals and rejections is also a major consideration requiring our attention. Unfortunately, unless s(he) develops a philosophical attitude, frustration will be intense. Many of the desirable character traits that contribute to an MD's success can become risk factors for depression when amplified by an apparent failure in a given case. Amongst the topics said not to receive enough attention in medical school are the psychological vulnerabilities of physicians. At least we should teach each other that it's "o.k." for a patient to say no!

A careful look at the special challenges created for the surgeon and internist by a Jehovah's Witness is exemplary of the subject under discussion. Members of that faith accept medical/surgical treatment but are deeply religious believing that transfusions of any autologous whole blood or components thereof is forbidden by several Biblical passages: "Only flesh with its soul — its blood — you must not eat" (Genesis 9:3-4); "you must pour its blood out and cover it with dust" (Leviticus 17:13-14); and "abstain from . . . fornication and from what is strangled and from blood" (Acts 15:19-21). Usually Witnesses recognize that such convictions can add risks to and complicate their care. Nevertheless, it's clear that they want/expect a voice in that care and hope that their physicians can understand an axiom: no one truly benefits if the corporal malady is cured at the price of compromising spiritual life with God.

Rather than bemoaning "this patient has tied my hands," some of us can choose to see the situation as only one more complication challenging our skill. All too often medical personnel are worried about their liability when they should be thinking about the patient's rights to make decisions about his body and his life.

Why does any of this matter? It matters because these principles, sometimes ethical and sometimes not, pervade medicine and can be critically important in the late stages of chronic disease. Once it becomes obvious that you are truly concerned, easily approached and listen well, you will find many patients who are ready to stop or forego a treatment. They've just been waiting for their physician to give them permission.

From Dr. Lucien S. Wilkins, a gastroenterologist in Wilmington.

A physician dealing with the issue of a patient's refusal to accept life saving treatment (e.g., blood transfusions) may be dealing with an age old issue involving patient's rights and physician's responsibility but the arena today is different as there are right-to-life groups, government agencies, legal precedents and disagreeing family members all wanting to be heard. The new arena increases the pressures, opens up options, but does not change the basic process of solution.

The solution is, in my opinion, straightforward: (1) communication, (2) education, and (3) consultation. I have intentionally omitted litigation, as that form of interference with the doctor-patient relationship should occur only when all reasonable solutions have failed.

Whole blood transfusion is controversial both on scientific and ethical grounds. Whole blood is a fixed dosage combination drug with potential side effects and a form of organ (blood) transplantation which opposes deep-seated religious beliefs of some.

Step one for the physician after hearing of the patient's refusal to accept the life saving treatment is to *sit down* with the patient and make certain you have clearly communicated the benefits and the consequences of the planned therapy.

If an impasse is still present, alternative, less objectionable therapies should be considered. Sometimes less therapy may be no less desirable. An alternative to transfusion might include i.v. saline to expand the volume, recumbency to decrease the need for volume, and iron for anemia.

If alternative therapies are considered not to be in the patient's best interest, the physician has two choices, either consultation or referral.

If referral occurs the physician may have solved his problem but the second physician is still at the same point in the decision making process. For either physician the next step is consultation. Ask for help!

Consult with a specialist in the problem area. A hematologist/oncologist, in the case of the patient who refused transfusion, would be most helpful as undoubtedly he has encountered this ethical problem before due to the nature of his practice. If a specialist is unavailable, go to your department chairman, who according to most hospital bylaws, is responsible for all practice matters within his department and should lend you support.

If your hospital is one of the 10% of American hospitals with an Ethics Committee composed of MDs, nurses, administrators, lay people, and hospital lawyers, you have a support system to assist you with your dilemma. They are there to support you in an ethical crisis in the same way the CPR team supports you in a medical crisis. They are not there to legislate ethics or to take the decision making away from the physician and the patient but to enhance the decision making process.

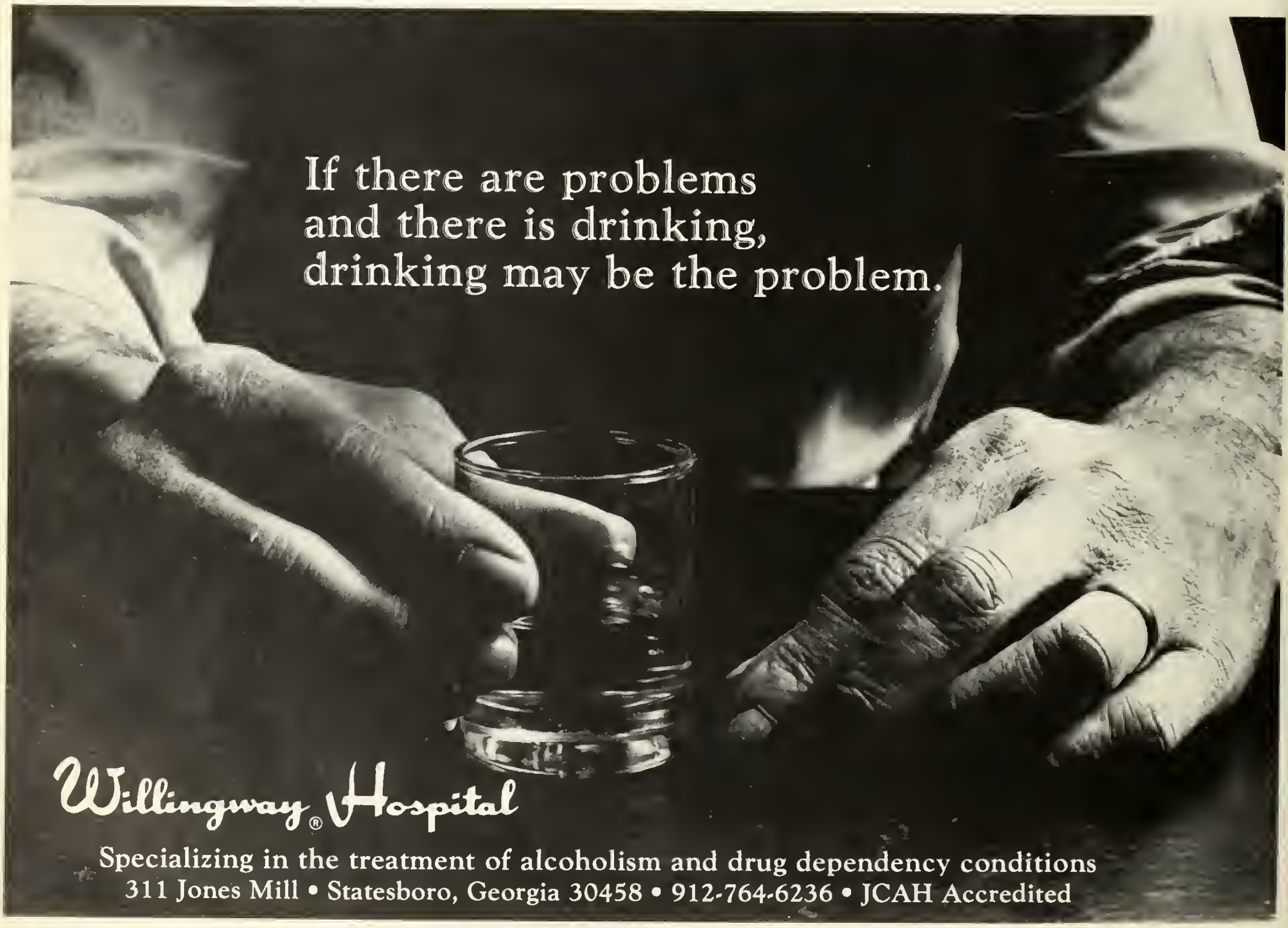
The above process may not solve the issue at hand but reaching a reasonable solution is more likely.

• EDITOR'S NOTE: Lots of good advice here, both philosophical and practical. The message seems to be to listen to the patient — not only his complaints, but also goals and values — before offering treatment. Sharing responsibility with patients will make some, but not all, decisions less difficult.

We are changing the format for the Forum slightly. Henceforth we will announce the next question of the month at the same time as we publish the responses to the current question. We invite readers to respond with opinions — short or long — to me. We will review them and publish as many as possible. We will also continue to ask others by mail to respond. We hope this will provide an even greater diversity of opinions for the Forum.

The next question for the Forum is "**In your personal opinion, does the refusal of precertification for admission to the hospital by insurance companies constitute the practice of medicine? Should they be held liable for malpractice?**"

May we have your response by February 22? Our address is Box 3910, DUMC, Durham 27710.



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North Carolina Medical Journal

Features for Patients February 1985

Welcome to the Helicopter Wars

The Development of a Helicopter Emergency Medical Service for Eastern North Carolina

Nicholas H. Benson, M.D., Christopher J. Mansfield, M.S. and
E. Jackson Allison, Jr., M.D., M.P.H.

As of the summer of 1984 there were approximately 80 hospitals in the United States with a helicopter emergency medical service based at their facility as part of an integrated trauma service and inter-hospital transport service for critically ill patients. These hospital-based helicopter emergency medical services (HEMS) typically involve the lease of a utility or executive helicopter retrofitted as an advanced life support (ALS) ambulance. The aircraft is operated and maintained by personnel supplied by a flight-service vendor but staffed with emergency medical personnel supplied by the hospital. The aircraft, pilot and medical team are stationed at the hospital and are immediately available to respond to trauma incidents or requests for the transfer of critically ill patients from one hospital to another on a 24-hour-a-day, seven-day-a-week basis. This paper relates the developmental process of such a service to serve the citizens of eastern North Carolina at Pitt County Memorial Hospital in Greenville.

Background

The first hospital-based program in the U.S. was initiated in 1972 at St. Anthony's Hospital, Denver, Colorado. The development of 80 or more similar programs in the ensuing 12 years is remarkable. In addition to the hospital-based programs, there are about ten privately-operated and four state-operated helicopter emergency medical service programs.

While services operated by Norfolk General Hospital (called "Nightingale") and Roanoke Hospital in Virginia provide some service to North Carolina residents within the effective range of their helicopters (70-100 miles), most of the citizens of North Carolina are without access to such a service. This is likely to change, however, as Pitt County Memorial Hospital and Duke University Medical Center are both in the process of developing hospital-based helicopter services. Other hospitals in North Carolina and many in other states are considering such a service. The state of North Carolina has designated a statewide task force to investigate the feasibility of creating a state-operated service.

Much can be learned from those who have gone before in this endeavor, and there has been a unique willingness on the part of personnel in existing programs to share their insights and experiences with individuals developing new programs. There is enough at stake financially, and there is sufficient complexity in developing a high quality service, for any hospital to be advised to proceed with cautious objectivity and thorough planning. While many hospital and medical personnel have had some tangential military experience with medical aviation, the development and administration of a complete program is not a simple task. (Unfortunately, the multitude of differences between military and civilian services makes expertise in the former of only marginal utility in the latter.)

Helicopters are expensive to buy ($.5-$1.5 million), operate and maintain. Their primary virtues are speed and access to areas not reachable by ground ambulances. They are neither medical nor therapeutic devices in themselves, but they can be used effectively to quickly extend a hospital's emergency medical and critical care capabilities to patients who are critically ill or injured. They

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From the Department of Emergency Medicine and the Center for Health Systems Research & Development, East Carolina University School of Medicine/Pitt County Memorial Hospital, Greenville 27834.

can quickly transport patients to and between the most appropriate resources of the health care system. The medical personnel who are carried to, or with, the patient are essential. They may be physicians, critical care nurses, paramedics, or respiratory therapists. A variable combination of any two of these health-care professionals may be carried on the helicopter, depending on mission and staffing patterns.

While most helicopters in EMS use are capable of carrying two or more patients, most missions transport just one patient. Data derived from a survey of 22 programs operating during 1982 suggest that two-thirds of all flights are hospital-to-hospital transfers; in one-third of flights the patient's origin is the scene of an accident.[1] The same data reveal that, regardless of origin, 44% are trauma victims, 15% are cardiac victims and 4% are burn victims. The remaining are critically ill medical, 20%; neonates, 13%; and high-risk obstetric, 4%.

The need for and efficacy of rapid intervention in critically ill patients are generally accepted. The need for and efficacy of rapid intervention in trauma cases have been extensively documented. Though the potential of death from trauma depends upon the severity of illness, timely intervention and quality of care are essential. **Time to treatment is a critical factor.** In the last 15 years there have been numerous reports and studies supporting the importance of rapid stabilization and definitive care. Stephany concludes that while 20% of all fatalities are instantaneous, 26% of all non-instantaneous deaths have a potential for survival; furthermore, fully half of these non-instantaneous deaths occur within the first 60 minutes after the accident.[2] R Adams Cowley, director of the Maryland Institute for Emergency Medical Services, draws similar conclusions and describes the **first 60 minutes as "the golden hour"** for delivery of trauma care.[3] Extensive experience by the military in Korea and Viet Nam support these findings for combat-related trauma.

The efficacy of the helicopter ambulance carrying personnel trained in advanced life support has been proven in both military and civilian applications. It serves both to bring more advanced medical care to the patient and to reduce time to definitive treatment, such as surgery. Experience of hospital-based helicopter ambulance programs during the last five years suggests that 20% of all patients transported by helicopter otherwise might have died,[4] which is similar to that in West Germany where a network of 32 air-rescue helicopters has been credited with a reduction in motor-vehicle mortality of 25 percent.[5] Baxt and Moody claim a 52% reduction in predicted mortality of patients transported by helicopter in San Diego.[6]

Helicopters are valuable only if the patient is transported to an institution capable of providing the appropriate level of care. Their value over ground vehicles increases in proportion both to the time saved in transport from site A to site B and to the level of care provided en route. The helicopter is of maximum use in linking the rural accident scene or hospital with the tertiary-care trauma center at a distance of 70 to 100 miles.[7]

The helicopter, because of its greater speed and the fact that it can travel in a straight line, can cover an area equivalent to that covered by 11 ground ambulances with response times equal to the helicopter.[8] Studies have shown that to equip and staff one ground ALS unit costs in excess of $175,000 per year.[4] If this figure is multiplied eleven times, the expense of a helicopter program can be less than that for corresponding equivalent ground coverage. If multiple Level I or Level II Regional Trauma Centers are also necessary for equivalent service, economic advantage increases in favor of the helicopter even more. Consideration of refining and maintaining skill levels of advanced cardiac and trauma life support personnel also is an argument against duplication.

The Planning Process

With the above understanding we were led to ask the questions "Could a hospital-based HEMS work in North Carolina?" and, more specifically, "Should there be a service for the eastern part of the state at Pitt County Memorial Hospital?"

Looking at the shape and size of North Carolina (500 miles East to West by 100-180 miles North to South) and considering the effective service area radius of a helicopter to be 70-100 miles, it was apparent that at least three programs would be necessary to cover the state geographically. Greenville happens to be about 100 miles from the easternmost portion of the state (Hatteras) and in the middle of a non-circular health service area (North Carolina Health Systems Agency VI) of 15,000 square-miles and 1.04 million people. Because of the geography and the fact that Pitt County Memorial Hospital (PCMH) is a Level II Regional Trauma Center and the site of the emergency medicine residency training program at the East Carolina University School of Medicine, it seemed logical that one of the HEMS programs should be at PCMH. However, could it be justified financially? Could the trustees of the hospital be convinced to support it?

Considering the population bases claimed as service areas of other programs as an initial rough indicator of need, we found that other programs served areas of as few as 95,000 people and as many as 10,500,000. The average was 1,500,000 per helicopter; thirteen of 59 programs (22%) had fewer than 1,000,000 in the service area.[1] A circular service area with a 100 mile radius for a HEMS program based in Greenville would contain well over 2,000,000, since the Research Triangle area and Wilmington would also be included (figure 1). It was decided that residents in the Research Triangle area would not likely be users (due to the proximity of local Level I Regional Trauma Centers at Duke and U.N.C.) but that some residents of New Hanover, Bladen, Pender and

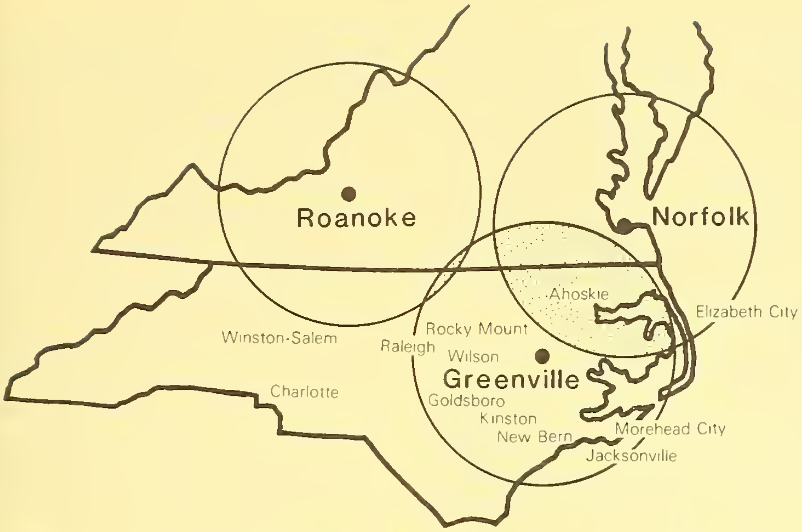

Figure 1. *A map of North Carolina and Virginia showing 100-mile radius circles around existent programs in Norfolk and Roanoke, Virginia and proposed program in Greenville, North Carolina.*

Sampson counties would; including these four counties as a secondary service area would add another 200,000 people to the proposed service area. However, it was apparent that some patients in the northeast portion of the state would continue to be served by the program in Norfolk; balancing the added utilization of a secondary service area against those patients lost to Nightingale from the sparsely-populated northeast resulted in a projected net service area roughly approximating the health service area of eastern North Carolina defined as NCHSA VI.

The feasibility study was undertaken (a) to estimate the cost of the proposed service; (b) to ascertain the demand for the service; (c) to estimate the revenues to be derived from accommodating that demand; (d) to compare cost with revenues; (e) to evaluate risks and indirect benefits; (f) to evaluate alternatives; and (g) to present it all within the context of the mission statements of Pitt County Memorial Hospital and East Carolina University School of Medicine.

Estimating the approximate cost of the service is relatively straightforward; estimation of demand is not so easy. A true needs assessment conducted in this area would involve the identification of the types of trauma and medical conditions that would benefit from rapid transport, defining the incidence of these conditions, applying them to the service area population and thereby estimating the need.

Some conditions that would be appropriate for transport by a helicopter might be:

1. Multiple trauma
2. Burns
3. Spinal cord/head injury
4. Distressed neonates
5. High-risk perinatal
6. Unstable cardiac problems
7. Unstable aneurysms
8. Intraaortic balloon pump patients
9. Streptokinase candidates
10. Reimplantation candidates
11. Organ transplant candidates
12. Other critically ill or injured persons

But no one knows the incidence of these conditions with enough accuracy to make estimates of need; nor do we have any accepted methodologies for defining what percentage would be realized demand, particularly in eastern North Carolina. The best we could do (and the best any other program sponsors have done to our knowledge) is to estimate demand based upon other programs' experiences.

Data of the American Society of Hospital-Based Emergency Air Medical Services (ASHBEAMS) and the Annual Program Statistical Survey published in Hospital Aviation[9] suggest that the mean utilization for 57 programs surveyed in 1983 was 63 patients transported per 100,000 population (the number of patients is roughly equal to the number of missions). The range of utilization was from 3 to 363 per 100,000 and the median was 43. Because of the extreme range, the median would normally be the most appropriate average to use but since 23% of the programs were new within the year and 47% were less than two years old with assumed lower utilization, the higher (mean) figure seemed appropriate to use as a guide for estimating the level of demand which would be experienced after the first year of operation in eastern North Carolina.

Applying this rate to a service area comprising all of eastern North Carolina (HSA VI) and having a population of 1,038,273 produces a projected utilization of 654 patients annually. Experience of other programs allows us to estimate that during the first year utilization will be about 60% of this figure (or 400 patients). Full utilization may be expected in the second year.

Of the 654 patients transported, we estimate that two-thirds (or 438) would be received at Pitt County Memorial. Of these, 80% would represent new patients, i.e., 351 new patients who would not have been admitted to PCMH otherwise.

Having arrived at some idea of volume of service to be provided, we then proceeded to identify the variables and determinants of revenues. Using information from existing programs, we estimated percentage source of payment and individual source collection rates. In the aggregate, we concluded that we might experience about 75% collection considering this to be a new program in North Carolina but trusting that significant precedent had already been set with similarly expensive ground transport. Assumptions also had to be made about how much we could charge for the service. Many of the existing programs charge substantially less than cost (typically about half) and make up the difference via their margin on additional inpatient revenue. Our inclination was to avoid the cost shifting and charge what the service would cost at projected full utilization ($1200-1300 per flight); to be safe, however, the break-even analysis was based upon a charge at only 75% of cost.

The cost was relatively easy to project and we figured it to be about $765,000 for the first year, 86% of which would be fixed costs representing a flight service lease and personnel commitments. Variable costs would be hourly use charges for the helicopter, fuel and supplies.

The break-even analysis was accomplished using an electronic spreadsheet and factoring in the effect of additional inpatient utilization with assumptions made about patients' length of stay and inpatient marginal cost. The electronic spreadsheet allowed considerations of many different combinations of assumptions about the variables. Trying all the worst-scenario assumptions about the variables used to create expenses and revenues, we were able to conclude that the program would be financially feasible.

Before proceeding, however, we reviewed and evaluated the alternatives to this endeavor. The possibility of equivalent service with multiple strategically placed ground ALS ambulances was ruled out on the basis of cost for PCMH to do this alone and lack of a consortium or regional entity to organize such an undertaking. The possibility of multiple trauma centers was also ruled out for similar reasons. The Military Assistance to Safety and Traffic (MAST) program was reviewed, but military priority and response times do not make this program an equivalent service in eastern N.C. Similarly, an aeromedical program within the state's law enforcement and/or transportation departments was considered but felt to be less desirable for the reasons of conflicting user priorities, response times and uncertainty of eventual development. Prevention was considered as an alternative, as well. While we know that most of the trauma and illness to be transported by helicopter is preventable and we feel strongly that it could be, society's resources and collective will have not been focused in that direction. Finally the risks and indirect benefits were reviewed.

The Development Process

Based upon the research related above, it was clear that a helicopter system would be extremely beneficial to the citizens of eastern North Carolina. It was viewed as a way of upgrading the ability to deliver high-quality advanced life support health care to critically ill and injured persons in the area, i.e., a way of extending the capabilities of the tertiary medical center to benefit the entire region. The hospital board received and reviewed our feasibility study; then they approved the program for a provisionary year, which is believed to be sufficient time to prove its medical and financial worthiness.

The Certificate of Need Application for the acquisition by lease of a helicopter service was submitted in May 1984. Having received approval from the Eastern Carolina Health Systems Agency in July 1984, we then awaited final approval from the North Carolina Department of Human Resources' Division of Facility Services, which was expected on or before October 28, 1984.

Working under the assumption that the CON would meet with approval, we next proceeded to deal with the process of selection of a vendor. Inasmuch as the vendor supplies the hospital with not only the medically retrofitted aircraft, but also the pilots, mechanic, scheduled and emergency maintenance, certain aspects of insurance coverage, and experience in marketing and program management, this is a decision of utmost importance to the success of the program. These vendors, for the most part, are involved with multiple civilian industries utilizing helicopters in addition to EMS work; these industries include logging, mining, rescue operations, fighting forest fires, and servicing off-shore oil rigs. The health-care area is a relatively new opportunity for involvement, having really developed over the past five to ten years. Some of them have extensive experience in hospital-based services; others have had only a few contracts for a limited period of time. While the former group brings years of experience and insight to the area, the latter group tends to offer lower bids to programs in the hopes of increasing the number of their hospital contracts. These factors of price to the hospital and experience of the vendor are of extreme importance. Further significant particulars include availability of "back-up" aircraft from the vendor (so that the program can remain operational when the hospital's helicopter requires maintenance), their maintenance record at other programs, the quality of mechanic and pilots they provide, and their administrative and financial solidity. In the final outcome, however, most public hospitals are still required to do a request for proposals and take the lowest bidder that meets their needs.

Selection of a particular helicopter for a program is yet another area that can be problematic. While this is much too complex a topic to discuss in detail here, some of the factors that need to be considered include the numbers of patients and attendants transportable; the speed, maneuverability and lift-power of the craft; the flying radius (without refueling); room in the aircraft for patient care; reliability; ease of maintenance; and cost. Some vendors, rather astutely, maintain that the hospital should work on medical parameters and marketing, leaving the choice of aircraft up to them; these authorities maintain that while the hospital officials are knowledgable in both medical matters and concerns about the local area, the vendor is the chosen representative of the helicopter industry and is more experienced in deciding which aircraft is best suited to local needs.

A third portion of the program that must be handled with great care to ensure a success is the flight team, i.e., those people who will deliver the health care in the air. A major decision in this realm is what types of professionals the team should consist of: physicians; physician-assistants; flight nurses; or paramedics. This decision will be made largely by preexistent realities. For instance, at PCMH there are not adequate numbers of physicians trained comprehensively in all aspects of critical care to staff both hospital and helicopter; nor do we have available to us paramedics with appropriate street experience. Thus, we have decided to fly two registered nurses; the exception to this is that flights for neonatal transports will use representatives of the hospital's standard neonatal transport team.

Selection of these flight nurses (FN), especially the chief flight nurse (CFN), requires a thorough search for persons with demonstrated excellence in critical care, an ability to react calmly and diplomatically in chaotic and stressful situations, strong experience in management and teaching, and a knowledge of prehospital care. These persons serve as extensions of the hospital's critical care units; they must be trusted to perform in an exemplary fashion under any conditions. Once selected, they need to undergo rigorous and comprehensive training to cover all aspects of the program; this includes, but is not limited to, advanced cardiac life support, advanced trauma care, cardiopulmonary emergencies, neurological crises, pediatric emergencies, high-risk obstetrics, altitude physiology, flight safety, extrication and immobilization, and radio communications. Part of this intensive training regimen should include onboard drills utilizing the equipment and cramped quarters of the aircraft. The quality of care that they deliver at a hospital or scene will have an overwhelming impact on whether the program gets further calls from that source.

Other principal members of the team must include a medical director with a strong background in emergency care, a program administrative director with agility in marketing, and dispatchers with EMT training to provide 24-hour staffing to a communications-dispatch center. (Note that often the CFN and the program director are the same person.) The team does not stop here, however; the program could be doomed to failure without the backing of the medical center's entire medical and nursing staffs, hospital administration, all ancillary departments, and all support personnel. All persons in the medical center community, from the chairman of the board of trustees to the groundskeeper who sweeps off the helipad, must lend their firm support.

A helipad close to the emergency department, a flight operations center (to include office space for staff and sleeping quarters for pilot), and a communications post with full UHF and VHF radio equipment along with equipment for continuous weather surveillance and recording of incoming calls and radio transmissions are vital.

While the flight team should be in nearly constant contact with medical personnel at the base hospital, it is necessary to have a complete set of policies and protocols to utilize as conditions dictate. This allows for appropriate care whenever radio contact might be lost, as well as assurance of adherence to a defined standard of care. It also provides guidelines to follow when the unforeseen arises; for example, what should the flight team do if they are on the way to another hospital to pick up a patient and they fly over a small plane which has crashed in a forest and no help for the pilot is in sight? Should they stop? Should they complete their primary mission?

The CFN and program director must create a system to maintain records of all aspects of all flights. This allows for evaluation by the CFN and the medical director of the quality of care rendered, data retrieval for audit and evaluation, appropriate follow-up reports to the referring agency and billing purposes. Since this is a relatively new dimension in health care, one of the unspoken requirements of all programs is to participate in research and data collection activities designed to justify the use of this high-cost modality and to ever-improve the quality of care available to all patients.

A recurring theme in advice from existing programs is one of marketing and public relations. Most programs start in an area that has never seen such a service before; therefore, it is incumbent upon the people in the program, even before they start taking patients, to illustrate to the potential referring agencies how and why they can aid them. This marketing may take many, many forms: presentations to hospital medical staffs; discussions with EMS, police and fire squads; displays at fairs, conventions and shopping centers; mailings of brochures, bumper stickers, telephone stickers, and buttons; participation in the electronic and print media; and outreach education programs on CPR, basic first-aid, etc. In addition to letting people know that the service exists, marketing must include information on how to access the service. People must know who can refer a patient, how to call the helicopter, and what types of patients are appropriate for the service. Beyond this, the potential referring agencies need to know where in their area a helicopter can land, how to make that landing area safe, and how to deal with the helicopter and crew during take-off and landing.

A positive public relations campaign is especially vital in dealing with local prehospital care providers. They must understand that the service is there to help them provide for a patient who is beyond their local capability, i.e., that the service is there to complement their abilities but not to supplant them. An image of help to the general community, of friendly and gracious cooperation with local agencies, and of delivery of excellent medical care to the critically ill or injured is paramount.

Conclusion

We received approval of our CON on October 26. Our request for proposals went out to the vendors in late August; the bids were opened in mid-September. We have filled the Chief Flight Nurse position, and we are now actively recruiting Flight Nurses. We hope to keep steadfastly to our timetable, which calls for initiation of training and coordination flights to referral agencies in early winter and availability for patient transport in early April 1985. In late September, PCMH was notified of the formation of a legislative study commission to investigate a statewide Highway Patrol-sponsored system with dual law enforcement-medical missions as a result of the statewide task force previously mentioned. At their final meeting in late November, this group decided to promote a bill to appropriate funds for the development of a statewide HEMS to be operated by the North Carolina Office of EMS.

The future of hospital-based EMS helicopters in this country is most promising and equally exciting. The number of programs shows potential for nearing 100 in a year or two. The proliferation of research and patient-care improvements should have a global impact on medical care. It becomes increasingly vital for programs to work together and to avoid competitive displays. Only through consistent and exhaustive evaluation of our methods and outcomes can this industry continue to strive to attain the excellence in patient care that is our goal.

The authors are deeply indebted to Ms. Joni Farmer for her ever-cheerful secretarial support.

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Duke Takes the Plunge

On March 1, 1985 Duke University Hospital will initiate a Helicopter Emergency Medical Service (HEMS). The helicopter will be based at the hospital, on a pad immediately adjacent to the emergency room entrance. Weather permitting, the helicopter will respond to calls 24 hours a day, 7 days a week.

On each flight, the helicopter will be staffed by a pilot and two nurses experienced in critical care or emergency services and specially trained for HEMS. While caring for patients in flight, they will be in constant contact with Duke physicians involved in the delivery and management of trauma and other critical care services.

The helicopter will be operated by a company chosen for its wide and successful experience in the operation of helicopters. The company will provide a Bell 222UT specially configured and equipped for EMS, pilots, a mechanic, maintenance, and a backup craft.

The service will transport patients who require immediate transfer to a tertiary care center. Typically these will be patients threatened with the loss of life, limb, or function as a result of

- life threatening trauma
- cardiac or respiratory emergencies
- acute pediatric medical emergencies
- acute surgical emergencies
- major thermal injuries

Patients will be transported to Duke Hospital, or to another tertiary care center when appropriate, feasible, and requested, and when the receiving hospital has agreed in advance to pay the cost of the flight.

The service will respond to calls coming in over a dedicated WATS line from other hospitals, from physicians, from police and emergency services, and other authorized agencies and individuals. The service will not compete with but will supplement ground ambulance transportation and other HEMS programs that may develop in North Carolina. It is anticipated that 80% of flights will transfer patients from other hospitals to tertiary care; the other 20% will evacuate patients from accident scenes and other points of need.

The Bell 222UT can fly more than 400 miles without refuelling, but the effective operating range of the service will be within 150 miles of Durham. Beyond that range, the advantage of the helicopter's speed (150 mph) is offset by distance. A range of 150 miles will allow service to 77% of North Carolina's population and all major cities except Asheville.

Operation of the service will cost $1.2 million per year. Variable cost — for helicopter operation, fuel, and supplies — will account for $200,000. Fixed costs — expenditures for nurses, pilots, dispatchers, a mechanic, maintenance, the helicopter, equipment, supplies, and administration — will make up the rest.

About 10% of these costs will be recovered through charges to patients for the helicopter service. For the balance, the hospital will draw on its other revenues.

Because of the expense and risks associated with the operation of an HEMS program, the decision to initiate a service at Duke required nearly a year of deliberation. In the end, the following considerations were paramount:

From Duke University Hospital, Durham 27710.

1. There is a clear and compelling need for responsive, reliable HEMS services in North Carolina. HEMS is a new field, and methodologies used to calculate the need for HEMS produce widely differing estimates, but it seems virtually certain that a program based in the Triangle area would make at least 300 flights per year.

2. The only existing service, which is provided when helicopters and crews are available from the Military Assistance to Safety and Traffic program at Fort Bragg, is clearly inadequate to the need and likely to reduce its services in order that military commitments can be met.

3. Duke is the kind of hospital where HEMS programs are most appropriately based. The hospital is a class I trauma center with comprehensive services in all nine trauma specialties and a wide range of critical, emergency, and intensive care services. The helicopter will extend Duke's services to patients now beyond reach, and it will bring to the hospital the very patients that our new facility is staffed and equipped to treat.

4. The operation of a HEMS program will create opportunities to expand training and research programs. Alone or in conjunction with other institutions, Duke operates thirteen different training programs in trauma, and the field is an area of growing research interest.

5. The operation of an HEMS program appears financially feasible. If cost and revenue assumptions prove accurate, the service will break even at a volume of 300 flights per year. It seems likely that the service will achieve that level of operation by the end of its first year.

6. The alternatives seem problematic at best. One is to wait for the development of a state-operated system, an idea that was first discussed in the early 1970s. In recent months there has been renewed discussion, but whether and when such a system would develop remain highly uncertain.

The other option we examined was the development of a shared service, to be operated by a new entity contracting with several hospitals. We eventually concluded that we could meet the objective of a shared service through arrangements to deliver patients to other tertiary care centers, without running the risks associated with creation and operation of a new enterprise functioning at the intersection of several hospitals.

Eventually we concluded that the hospital could and should initiate a Helicopter Emergency Medical Service, and we all look forward to the initiation of patient flights on March 1.

Duncan Yaggy, Ph.D.

North Carolina Baptist Hospital's Position

North Carolina Baptist Hospital supports the concept of a state-supported helicopter ambulance service to serve the people of North Carolina. Furthermore, when the decision is made to place such a service in the western region of North Carolina, the first such undertaking ought to be at Winston-Salem's Baptist Hospital. There are several compelling reasons for that. The hospital has the western region's only level one trauma center. It has extensive experience, in cooperation with Forsyth Memorial Hospital, in the transportation and care of high risk pregnant women. Its intensive care nursery serves all of North Carolina as well as surrounding states. Its burn unit is a vital resource for northwest North Carolina. And a significant portion of North Carolina's population lives within a short flying distance of the Bowman Gray/Baptist Hospital Medical Center.

Richard M. Heriot

From 300 South Hawthorne Road, Winston-Salem 27103.

North Carolina Memorial Hospital's Position

The North Carolina Memorial Hospital continues to support the concept of a statewide coordinated network for the provision of aeromedical transportation for patients requiring such services. The Hospital supports and endorses the recent recommendation of the Legislative Study Commission which recommends that the State of North Carolina establish such a network under the aegis of the Emergency Medical Services Division of the Department of Human Resources. It is the position of NCMH that such a public service would assure equal access to all North Carolinians. A comprehensive statewide system would also nicely link existing ground transportation, hospital emergency rooms, trauma centers and air transportation in the most cost effective manner possible. In the event that such a statewide system is not established, the North Carolina Memorial Hospital would then intend to establish its own hospital-based, aeromedical transportation capability in order to meet the unique needs of its regional burn center, neonatology center and other tertiary and educational programs which exist to serve the state of North Carolina.

Eric B. Munson

Editor's Note: North Carolina Memorial Hospital has hedged its bets by filing a Certificate of Need for a helicopter service with the appropriate authorities.

From the University of North Carolina, Chapel Hill 27514.

Vitiligo

Russell W. Eyre, M.D., Claude S. Burton, M.D., and J. Lamar Callaway, M.D.

Vitiligo comes from the Latin word vitium which means blemish. These white spots affect at least one out of every 100 people. All races are affected but the white spots are more disfiguring in darker races. Skin color is determined by the mixture of three pigments. Melanin, a complex polymer, is produced by pigment cells or melanocytes. Melanocytes are absent in the white spots of vitiligo. Two other pigments combine in the white spots to give the remaining color. Hemoglobin, a blood pigment, is red when combined with oxygen and blue after it releases oxygen to the tissues. Plants such as carrots may deposit a yellow pigment, carotene, in the skin of people who eat a lot of yellow vegetables.

A Wood's lamp, or black light, is an essential tool in the clinical evaluation of any white spot. This lamp produces ultra-violet light that enhances superficial pigment changes. The ultra-violet rays don't penetrate into the skin as far as visible light rays so superficial changes are enhanced and deeper changes are decreased. The white spots of vitiligo appear porcelain white when examined with the Wood's lamp. Another cause of white spots, tinea versicolor, which is produced by a superficial fungus infection, glows yellow in "black light." Leukoderma, or white spots, after an inflammation in the skin are usually less evident with a Wood's lamp examination. Any leukoderma should also be tested for sensation with a pin-prick to rule out leprosy.

A careful total body examination with a Wood's lamp of a patient who complains of one white spot often reveals several other less obvious spots. Exposed skin is most commonly affected, especially around the eyes, nose, and mouth. Spots are usually several inches in diameter and circular but they may grow together so that the entire skin appears bleached. The edges of the patches of vitiligo sometimes show a gradual color change from white to brown producing a three color pattern. The peak incidence occurs at 20-30 years but all ages have been affected.

The cause of vitiligo is unknown. Occasionally the onset will follow an emotional upset or the white spot may follow the course of a nerve. This leads some to believe that a substance produced by nerves is responsible for destroying the melanocytes. Vitiligo may appear after an injury or sunburn. Perhaps the immune system is exposed to parts of the melanocyte after those injuries that it usually doesn't see thus immunizing itself against the melanocyte. Other autoimmune diseases where the immune system destroys other cells are more common in patients with vitiligo. Thyroiditis, diabetes, pernicious anemia, alopecia areata, and adrenal insufficiency are all seen more commonly in patients with vitiligo. Rarely someone with malignant melanoma may present with only vitiligo. A careful history and physical examination should be done to rule out these diseases. It is not cost effective to order screening laboratory tests without some clue in the history or physical examination because although the incidence of these other autoimmune diseases is increased they are still quite rare.

Treatment is not always necessary especially if the patient is light skinned and will avoid tanning or if the spots may be easily concealed with clothing. The spots of vitiligo will burn very easily in the sun because melanin, a very effective sunscreen, is missing in them. Several excellent cosmetic products are available that provide cover-up and protection. Cover Up or Dermablend are two good products. Artificial suntan creams contain a dye, dihydroxyacetone aniline, that will stain the white spots but it is difficult to match the surrounding skin tones. A topical steroid cream has helped some patients but it isn't generally useful. If the pigment loss is extensive, permanent bleaching of the normal skin may produce the best cosmetic result. Monobenzylether of hydroquinone is applied to the skin for several months to cause complete loss of melanin.

Over three thousand years ago the ancient Egyptians discovered the most effective treatment for vitiligo. They found that when certain plants were either eaten or rubbed into the skin and the patient then exposed himself to sunlight the white spots would often disappear. These plants have high concentrations of chemicals called psoralens. Psoralens in combination with ultra-violet light can repigment over half of the patients with vitiligo. Unfortunately several years of treatment may be necessary to fully repigment someone and the treatments are not without risks. Skin cancers and cataracts are increased in patients exposed to this treatment. It is very easy to severely burn and blister the white skin with these treatments. The normal skin becomes more tanned which makes the white spots more noticeable. Despite these cautions it is the most effective and widely used treatment for vitiligo.

Drastic treatment measures are sometimes used in India, where patients with vitiligo are social outcasts. Cyclophosphamide, a drug used to treat cancers, has recently been used in low doses to treat some patients with vitiligo. Most patients had a very good response. Sadly this drug has been found to cause a second malignancy, usually a leukemia, in a high percentage of those patients who have taken it. A malignancy is a high price to pay for treatment of a cosmetic problem. We hope future studies of the pigment process will reveal an effective, safe treatment for this distressing disease.

From the Division of Dermatology, Department of Medicine, Duke University Medical Center, Durham 27710.

Pervasive Procrustianism — Isopropyl Alcohol Intoxication

Ronald B. Mack, M.D.

- *Shakespeare probably didn't refer to isopropyl alcohol poisoning when he wrote, "Aye, there's the rub," but rubbing alcohol can, indeed, do you in.*

MANY medical students, some House Staff and a "rare" practitioner (surely you jest!!) would like to see diseases in neat packages — just as it says in the textbook. We more "mature" physicians realize that medicine is not quite that simple — diseases do not present in the patient exactly as the literature describes. In a similar argument, just because a patient swallows an "alcohol" in overdose you should not assume that all alcohols ingested in overdose behave and are to be treated as ethanol intoxication. The desire to make the clinical features fit the diagnosis (even if they do not) or to treat all alcohol overdoses the same (even if the alcohols are different) can be called *procrustianism.* If you persist in such thinking and cause damage to your patients thereby, you are guilty of pervasive pernicious procrustianism. What's in a name?

The condition is properly named for Procrustes. This ancient Greek was a robber of great fame and skill. He also gave new meaning to the word hospitality. It was the custom in those days to invite people to your house, including strangers, for a meal and a bed for the night. This malevolent robber tied his victims to the bed. Sad to say, Procrustes was a compulsive fellow; if the invited guest did not quite fill up the space in the assigned bed, our host would stretch the invitee until he fit the bed. If by chance the guest was too big for the bed (perish forbid), Procrustes would cut off those parts of the person required to produce a perfect fit. (Does this remind you of a hotel you once stayed at in Cleveland?)

The subject at hand today is isopropyl alcohol (AKA isopropanol) poisoning. Using the phrase "at hand" seems to be a good idea as this product is most popularly known as "rubbing alcohol." This aliphatic alcohol is used quite extensively in industry but for the average consumer it is used most commonly as a rubbing solution or as a disinfectant but also can be found in skin lotions, hair tonics, de-icing and anti-freeze products and window cleaning solutions. For home use it is typically sold in pint bottles and it possesses a distinct odor. This alcohol is not uncommonly substituted by the non-discriminating alcoholic when the good stuff is not available. You are probably more apt to be called upon to manage a patient who swallowed isopropanol accidentally or in a suicide attempt.

The absorption of isopropyl alcohol after ingestion is quite rapid, usually within one-half hour (with very large ingestions absorption may take considerably longer). This substance is distributed in body water and has a volume of distribution (V_D) about 0.58-0.70 L/kg (goody!! — could be dialyzed if the situation turns ugly). Once ingested and absorbed per the GI tract, the liver assumes control and becomes the main site of isopropanol's metabolism. The enzyme alcohol dehydrogenate metabolizes this alcohol to *acetone* (do not forget this and also please remember this does not refer to fingernail polish remover). Other ketoacids, i.e., aceto-acetic and hydrobutyric, are fortunately not produced. The end result of this enzymatic metabolism is 80% excreted as acetone and 20% excreted as unchanged. The final word on the toxicokinetics of this alcohol has not been worked out but seems to be most likely related to *first order kinetics* (the rate of transfer, i.e., metabolic breakdown, is directly proportional to the amount of the drug remaining — remember? How many times do I have to tell you that!!). Both the acetone and the unchanged isopropyl alcohol are excreted primarily in the urine.

This seems to be a good place to talk down about the dangers of *inhaling* isopropyl alcohol. For many decades (and even as we speak) this substance has been advised for the purpose of fever reduction. The literature is filled with articles on the therapeutic benefits of rubbing alcohol on the fevered patient, usually a child, in an effort to produce defervescence. I recently saw a piece of literature printed by a prominent drug company that promotes their antipyretic and also advises on the use of isopropyl alcohol "sponging." This type of anachronistic advice must cease forthwith. Strangely enough it is not the "sponging" per se that can cause intoxication because skin absorption of isopropyl alcohol does not seem to be significant. However, isopropanol vaporizes quite readily and is absorbed through the lungs with ease. Therefore, using this method of fever reduction, especially in a poorly ventilated room, can have evil consequences such as intoxication and coma. Also, it

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From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

has been reported recently that isopropyl alcohol has the potential to produce a chemical burn when applied to the skin of severely premature infants, e.g., when used as a disinfectant.

Just how much of this stuff can you imbibe and still live? Well, it is believed that as little as 20 ml can cause symptoms and an 8 ounce glassful is considered to be a potentially lethal dose for an adult. The toxic dose is estimated to be about *1 ml/kg* of 70% (the usual %) isopropyl alcohol. This amount produces a serum isopropanol level of 70 mg/dl. Concentrations of 50-100 mg/dl produce symptoms and levels of 150-200+ mg/dl can cause coma and death. Certainly these levels of ethanol would not usually kill; however isopropyl alcohol is different — the central nervous system depressant effects are about *twice those of ethanol* at comparable blood levels. (Is this because of the acetone produced during the metabolism of isopropanol?) Peak serum levels are reached in about one hour and any level > 50 mg/dl requires careful scrutiny by health care professionals.

It seems quite clear by now that isopropyl alcohol, because of rapid absorption, can cause adverse symptomatology quite soon after ingestion — typically within 30 minutes. The earliest complaints are apt to be gastrointestinal, manifested by pain, secondary to the gastritis and vomiting, often bloody, as well as diarrhea. The CNS seems to be hit rather decidedly from ingestion of this substance and the patient can expect to experience headache, confusion, dizziness, ataxia, stupor or deep coma. The coma produced can be quite profound and may be partially due to the formation of acetone that occurs during the metabolism of isopropanol. The thermal regulatory centers in the CNS plus peripheral vasodilatation can produce hypothermia which can be a frightening prospect indeed. If all of this was not bad enough, large ingested doses can cause myocardial depression and hypotension. The combination of *coma* and *hypotension* in a patient with isopropyl alcohol ingestion portends evil — the prognosis decreases remarkably when these two findings coexist. The pupils are typically *miotic* and this fact sometimes helps in making the differential diagnosis. Hepatic involvement can lead to hypoglycemia; a similar phenomenon occurs, not uncommonly of course, in children who ingest ethanol.

Many authorities believe that blood isopropyl alcohol levels are the best laboratory markers for the seriousness of the poisoning and gas chromatography seems to be the way to determine these levels. To help in the diagnosis it is well to remember that this alcohol imparts a distinctive odor to the patient's breath and so does the acetone and that the urine contains large amounts of ketones without glycosuria and usually without metabolic acidosis. Severe toxicity produces an anion gap greater than 12 mEq/l as well as an increase in serum osmolality. These latter two tests may be helpful in diagnosis and management when serum isopropyl alcohol levels are not readily available (and for most of us they are not immediately available). Thus if you have a patient, young or old, who is very confused or comatose, with acetonuria and without glycosuria (or hyperglycemia) who is not starving, etc. think of an acute isopropanol ingestion.

The treatment in isopropyl alcohol intoxication is somewhat tricky — there is no antidote of course and the usual poisoning supportive measures are either not useful or contraindicated. If the patient is alert and it's very early in the course, gastric emptying, via ipecac syrup, seems quite proper. In the most obtunded patient, gastric lavage is the way to go. In fact, some authors suggest intermittent or continuous lavage in such patients because isopropyl alcohol can be transported out of the blood back into the stomach. Whether to use activated charcoal or not is debatable; it is not effective in absorbing this alcohol but, on the other hand, it does no harm. Forced water diuresis does not seem to help either. It is imperative to support and maintain the vital signs which go awry in this poisoning. Ice water lavage (a Yankee trick) can be utilized to ameliorate gastric bleeding. The final question in the management of a patient severely intoxicated from isopropyl alcohol is whether or not you should institute dialysis and if so, when. This chemical would appear to be the answer to a dialyzer's dream, i.e., low plasma protein binding, low volume of distribution, etc. It appears that if you must use dialysis use hemodialysis. At present the best candidates for hemodialysis are those with hypotension not responding to simpler methods and those whose serum levels exceed 400+ mg/dl. Please bear in mind that because of this alcohol's slow metabolism the adverse clinical effects can last for two to four times those of ethanol.

By the way, be sure to drop in when you are in the neighborhood. I'm sure you would *fit in perfectly*.

Angina comes in many forms...

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See following page for brief summary of prescribing information.

SORBITRATE®

(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent Cutaneous vasodilation with flushing may occur Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined *The oral controlled-release forms of isosorbide dinitrate should not be chewed*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg)

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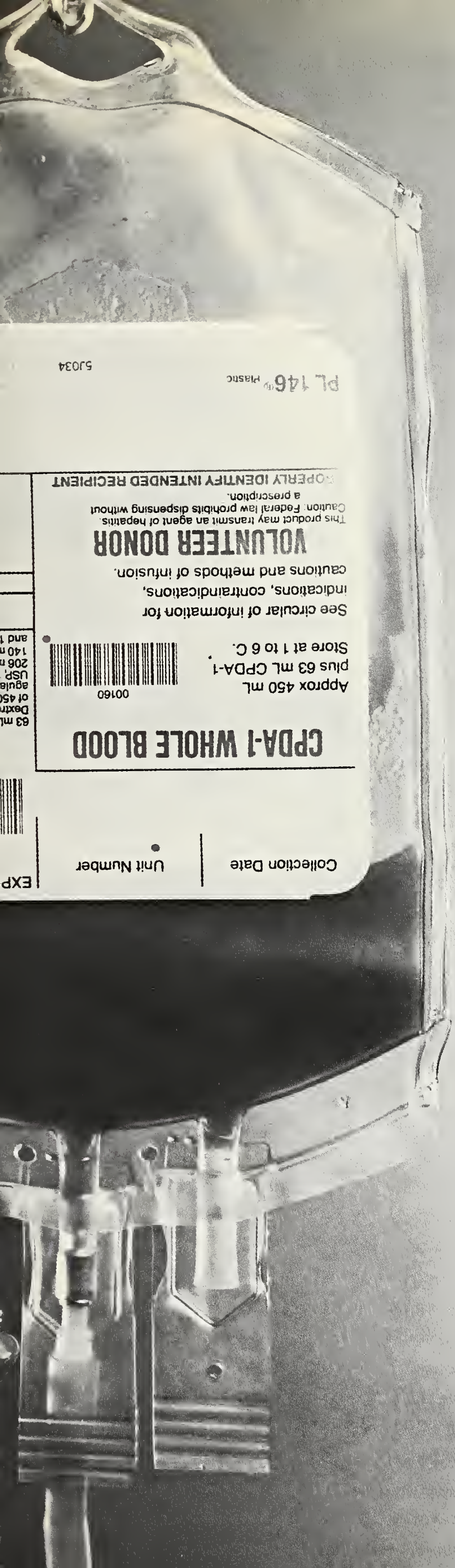

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For further information about Charter Hills or admission procedures, contact:

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William R. Bodner, Jr., M.D.
Hospital Administrator: Harold Small

Charter Mandala Hospital

3637 Old Vineyard Road
Winston-Salem, North Carolina 27104
(919) 768-7710

Beds: 72
Psychiatric Staff: 12
Programs: Adult and Adolescent Psychiatric; Adult and Adolescent Addictive Disease

For further information about Charter Mandala or admission procedures, contact:

Medical Director: Bruce W. Rau, M.D.
Hospital Administrator: Harold Small

Charter Pines Hospital

3621 Randolph Road
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Beds: 60
Programs: Adult and Young Adult Psychiatric

Scheduled to open in February 1985

For further information about Charter Pines contact:

Medical Director:
R.Gordon Crandall, M.D.
Hospital Administrator: Stan Hilliard

Charter Northridge Hospital

400 Newton Road
Raleigh, North Carolina 27619
(919) 847-0008
1 (800) 447-1800

Beds: 66
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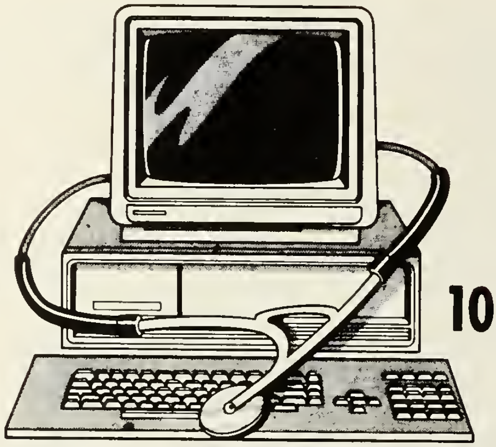

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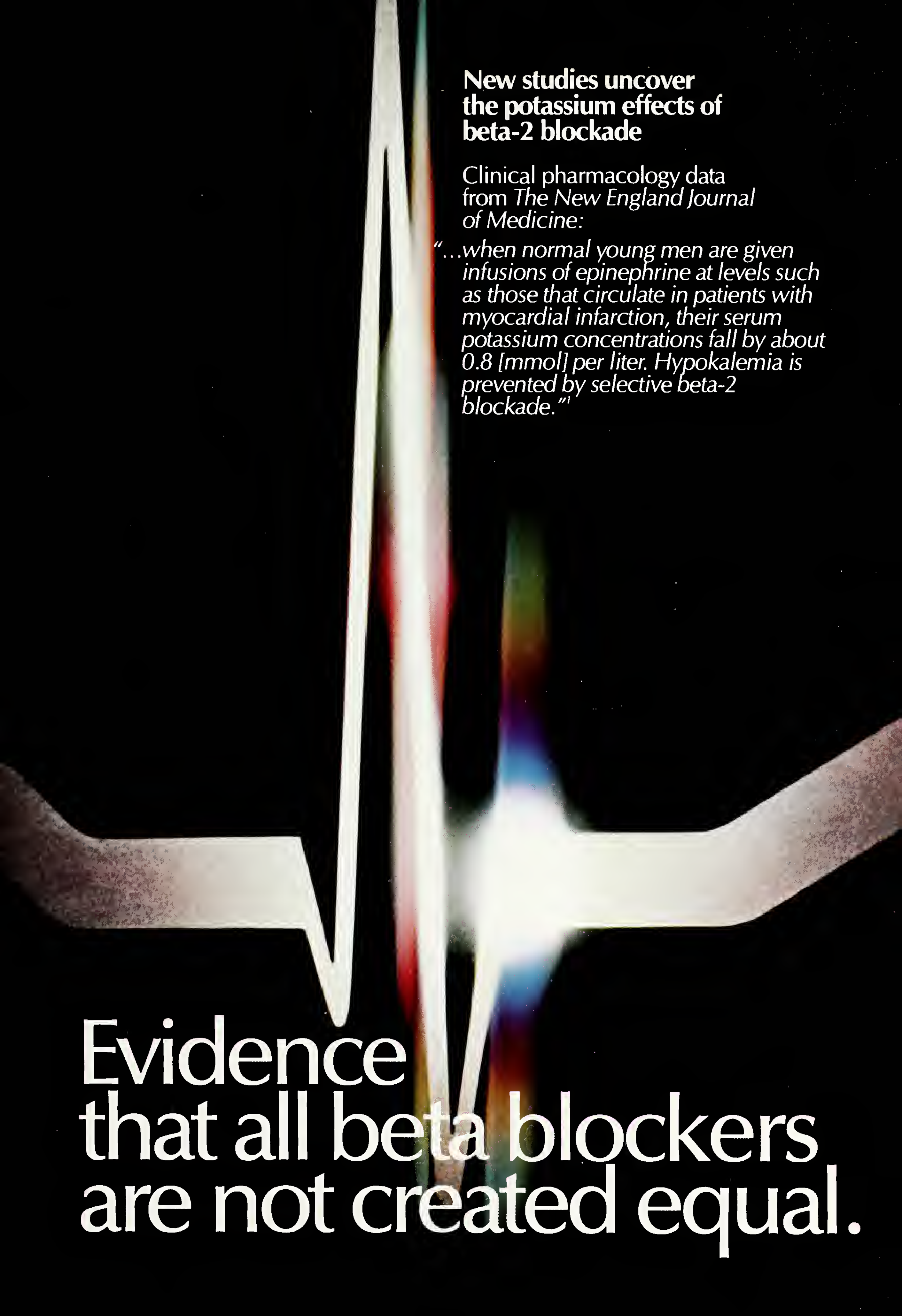

New studies uncover the potassium effects of beta-2 blockade

Clinical pharmacology data from *The New England Journal of Medicine:*

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 [mmol] per liter. Hypokalemia is prevented by selective beta-2 blockade."[1]

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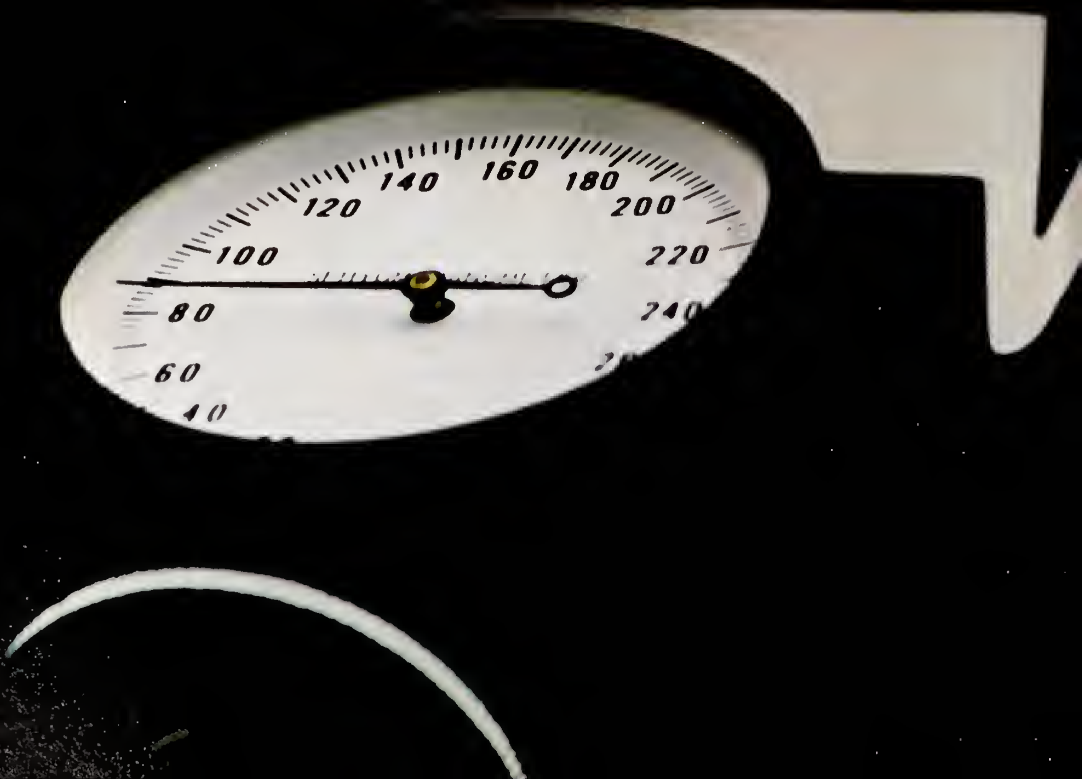

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Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[2,3] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree., and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily
INDERAL® LA
(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Please see brief summary of prescribing information on the next page for further details.

For beta-1/beta-2 blockade **Once-daily**

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use Effects on plasma volume appear to be minor and somewhat variable INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmias is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient But there are also situations in which sympathetic stimulation is vital For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm

Propranolol is not significantly dialyzable

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of be receptor agonists and its effects can be reversed by administration of such agents, e dobutamine or isoproterenol However, such patients may be subject to protracted seve hypotension Difficulty in starting and maintaining the heartbeat has also been reported w beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the a pearance of certain premonitory signs and symptoms (pulse rate and pressure changes) acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be mo difficult to adjust the dosage of insulin

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidis Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptor of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tes

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have be reported in which, after propranolol, the tachycardia was replaced by a severe bradycard requiring a demand pacemaker In one case this resulted after an initial dose of 5 r propranolol

PRECAUTIONS. *General* Propranolol should be used with caution in patients with impair hepatic or renal function INDERAL (propranolol HCl) is not indicated for the treatment hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patier should be told that INDERAL may interfere with the glaucoma screening test Withdrawal m lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart diseas elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as res pine should be closely observed if INDERAL is administered The added catecholamir blocking action may produce an excessive reduction of resting sympathetic nervous activ which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthosta hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals ha been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significa drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosa levels Reproductive studies in animals did not show any impairment of fertility that w attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic animal studies at doses about 10 times greater than the maximum recommended human dos

There are no adequate and well-controlled studies in pregnant women INDERAL shou be used during pregnancy only if the potential benefit justifies the potential risk to the fetu

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised wh INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and ha rarely required the withdrawal of therapy

Cardiovascular bradycardia, congestive heart failure, intensification of AV block, hyp tension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of t Raynaud type

Central Nervous System lightheadedness, mental depression manifested by insomn lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visu disturbances, hallucinations, an acute reversible syndrome characterized by disorientation time and place, short-term memory loss, emotional lability, slightly clouded sensorium, ar decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhe constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with achi and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytoper purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has be reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male imp tence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactio involving the skin, serous membranes and conjunctivae reported for a beta blocker (practol have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride ir sustained-release capsule for administration once daily If patients are switched from INDER tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeu effect is maintained INDERAL LA should not be considered a simple mg for mg substitute f INDERAL INDERAL LA has different kinetics and produces lower blood levels Retitration m be necessary especially to maintain effectiveness at the end of the 24-hour dosing interv

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 n INDERAL LA once daily, whether used alone or added to a diuretic The dosage may t increased to 120 mg once daily or higher until adequate blood pressure control is achieve The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 6 mg may be required The time needed for full hypertensive response to a given dosage variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL l once daily, dosage should be gradually increased at three to seven day intervals until optimu response is obtained Although individual patients may respond at any dosage level, tl average optimum dosage appears to be 160 mg once daily In angina pectoris, the value ar safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few wee (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL l once daily The usual effective dose range is 160-240 mg once daily The dosage may t increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is n obtained within four to six weeks after reaching the maximum dose, INDERAL LA thera should be discontinued It may be advisable to withdraw the drug gradually over a period several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are to limited to permit adequate directions for use

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LEARNING WITHOUT WORDS

Adult Circumcision and Diabetes

Christopher M. Justis (MLS) and Edward O. Janosko, M.D.

- *Diabetes mellitus occurs significantly more often than expected in patients presenting for circumcision for balanitis and phimosis.*

THE relationship between patients requiring circumcision and diabetes mellitus has not been generally appreciated. A search of the literature reveals only two significant papers studying this relationship.[1, 2] We have been impressed with the prevalence of newly diagnosed diabetes mellitus found in patients requiring circumcision for balanitis and phimosis, and the prevalence of previously diagnosed diabetes mellitus in patients presenting for circumcision. We explored this relationship in a retrospective study of patients who underwent circumcision.

Materials and Methods

The records of 234 men ≥ 15 years old who underwent circumcision by the physicians of Greenville Urology Clinic between January 1976 and June 1984 were retrospectively reviewed; 208 of these patients had the diagnosis of phimosis, balanitis or both (table 1).

The remainder of the patients had other miscellaneous diagnoses of herpes genitalis, condyloma accuminata, carcinoma, frenular bands, congenital phimosis and others (table 2).

The presence or absence of diabetes mellitus was recorded. Patients were considered known diabetic if they were currently under a physician's care for previously diagnosed diabetes. Patients were considered new diabetics when, after they were found to have glycosuria on dip stick at our office and were subsequently referred to their physicians, they were found to have documented diabetes. The age of the patients was also recorded.

From the Section of Urology, Department of Surgery, East Carolina University School of Medicine, Greenville 27834.

Table 1

Dx. at Surgery	No. of Patients	Known Diabetics	New Diabetics	Prevalence Diabetics (%)	Prevalence New Diabetics (%)
Phimosis	90	8	2	11.11	2.22
Balanitis	82	10	3	15.85	3.65
Both	36	6	8	38.88	22.22
Total	208	24	13	17.78	6.25

Table 2

Dx. at Surgery	No. of Patients	Known Diabetics	New Diabetics	Prevalence Diabetics (%)	Prevalence New Diabetics (%)
Herpes	1	0	0	0	0
Condyloma accuminata	2	0	1	50.0	50.0
Cancer	2	0	0	0	0
Congenital phimosis	11	0	0	0	0
Penile implant	1	1	0	100.0	0
Sebaceous cyst	1	0	0	0	0
Circumcision revision	1	0	0	0	0
Frenular tear	2	0	0	0	0
Frenular band	2	0	0	0	0
Sinus tract	1	0	0	0	0
Skin graft	1	0	0	0	0
Ulcer, nonspecific etiology	1	0	0	0	0
Total	26	1	1	7.6	3.84

Table 3

Age of Patient	No. of Patients	Diabetes	Known Diabetes	New Diabetes	Prevalence Diabetes (%)	Prevalence New Diabetes (%)	Expected Prevalence Diabetes (%)*
25	75	73	2	0	2.66	0	.12
25-44	100	86	9	5	14.00	5.00	.62
45-54	24	13	5	6	45.83	25.00	1.54
55-64	17	10	6	1	41.17	5.88	3.20
64-74	11	8	3	0	27.27	0	4.71
75	7	5	0	2	28.57	28.57	4.70
Total	234	195	25	14	16.66	5.98	1.05

* U.S. National Center for Health Statistics: Characteristics of Persons With Diabetes. U.S. July 1964-June 1965 Washington, D.C.: United States Department of Health, Education, and Welfare, Public Health Service Publication, Series 10, No. 40 1967.

Results

Of the 234 patients, 39 had diabetes mellitus yielding an overall prevalence of 16.6%. Of these 39 patients, 14 were previously undiagnosed as having diabetes mellitus yielding a prevalence rate of newly diagnosed diabetes of 5.98%. It is interesting that 12 of the 14 new diabetics were diagnosed between the ages of 31 and 64.

Of the 208 patients with balanitis and/or phimosis, who comprised 88.88% of patients in the study, 37 had diabetes mellitus, an overall prevalence of 17.78% and 13 of these were newly diagnosed diabetics, a prevalence rate of 6.25% (table 1).

Table 3 summarizes the population study by age, whether diabetes was present or not, the prevalence of newly diagnosed diabetes, and the expected prevalence of diabetes mellitus in the general male population.[3]

Using Chi-Square statistical analysis, there is a significant increase in the prevalence of diabetes mellitus in all patients in our study ($p < .001$) and in patients with the diagnosis of balanitis and/or phimosis ($p < .001$), when compared by age with that expected in the general male population (see Appendix).[3]

Discussion

The dermatologic manifestations of diabetes mellitus, which are well documented, include balanitis and phimosis.[4] In 1973 Cates and Associates studied 156 patients undergoing circumcision, of whom 110 had recent phimosis.[1] Of these latter patients, 35 had diabetes mellitus and 26 of these were newly diagnosed. He concluded in his study that patients over 18 years of age with recent onset phimosis had 31% prevalence of diabetes mellitus. Later, in 1982, Chopra and Associates found a prevalence of 36.1% for diabetes in 110 patients presenting with recent onset of phimosis. In our study of 234 patients undergoing circumcision for a variety of indications, there is a significantly increased prevalence ($p < .001$) of diabetes mellitus than expected.

The majority of these circumcised patients (88.88%) presented with phimosis and/or balanitis. The prevalence of diabetes in this latter group was 17.78%, almost 17 times higher than the prevalence found in the general male population.[3]

Since our method of screening for diabetes mellitus may yield false negative results in patients who are not glycosuric at the time of presentation, our statistics represent a minimal estimate of the presence of diabetes in patients requiring circumcision. Our results confirm the studies of Cates and Chopra that a relationship exists between diabetes mellitus and balanitis and phimosis. Adult males who present with balanitis and/or phimosis should be screened for diabetes mellitus. A careful history for symptoms of diabetes and the urine dip stick for glycosuria, which can provide a reliable indication of the disease, should be the minimal office screening procedures performed.[5, 6]

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Appendix

The statistics obtained for the general reference male population were obtained from the study of 134,000 persons interviewed by the Division of Health Interview Statistics of the U.S. Census Bureau. Persons were considered diabetic if they knew they were diabetic and on the follow up detailed supplemental questionnaire were investigated as far as their diabetic history, diagnosis and medical treatment.[3]

EXCLUSIVE

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Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone

> TALWIN® Nx is intended for oral use only Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances (See **Drug Abuse and Dependence** section.)

Warnings: *Drug Dependence* Can cause physical and psychological dependence (See **Drug Abuse and Dependence**) *Head Injury and Increased Intracranial Pressure* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention, these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure Can obscure the clinical course of patients with head injuries, in such patients, use with extreme caution and only if deemed essential *Usage with Alcohol* Due to potential for increased CNS depressant effects, alcohol should be used with caution. *Patients Receiving Narcotics* Pentazocine is a mild narcotic antagonist Withdrawal symptoms have occurred in patients previously given narcotics, including methadone *Certain Respiratory Conditions.* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis

Precautions: *CNS Effect.* Use cautiously in patients prone to seizures, seizures have occurred though no cause and effect relationship has been established Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours Such patients should be very closely observed and vital signs checked, if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur. *Impaired Renal or Hepatic Function.* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects, it should be administered with caution in renal or hepatic impairment. In long-term use, precautions should be taken to avoid increases in dose by the patient *Biliary Surgery* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures, the clinical significance of these findings is not yet known. *Information for Patients* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants. *Myocardial Infarction* Use with caution in patients with myocardial infarction who have nausea or vomiting *Drug Interactions. Usage with Alcohol* See **Warnings**. *Carcinogenesis, Mutagenesis, Impairment of Fertility* No long-term studies in animals to test for carcinogenesis have been performed *Pregnancy Category C* Should be given to pregnant women only if clearly needed *Labor and Delivery* Use with caution in women delivering premature infants Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown. *Nursing Mothers* Caution should be exercised when administered to a nursing woman *Pediatric Use* Safety and effectiveness in children below the age of 12 years have not been established

Adverse Reactions: *Cardiovascular* Hypotension, tachycardia, syncope. *Respiratory* Rarely, respiratory depression *CNS Acute CNS Manifestations.* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted. *Other CNS Effects:* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor. *Gastrointestinal.* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress *Allergic:* Edema of the face, dermatitis, including pruritus, flushed skin, including plethora *Ophthalmic* Visual blurring and focusing difficulty *Hematologic.* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia *Other:* Headache, chills, insomnia, weakness, urinary retention.

Drug Abuse and Dependence: *Controlled Substance* TALWIN Nx is a Schedule IV controlled substance

Dependence and withdrawal symptoms have been reported with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported. In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient Tolerance to the analgesic effect is rarely reported, there is no long-term experience with oral use of TALWIN Nx

The amount of naloxone present (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine; however, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals

Overdosage: *Treatment* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated Assisted or controlled ventilation should also be considered For respiratory depression, parenteral naloxone is a specific and effective antagonist

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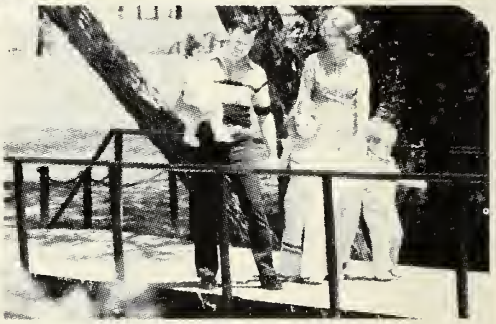

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NEWS FROM CDC

Delta Hepatitis — Massachusetts

An outbreak of hepatitis B (HB) that began in September 1983 is continuing in Worcester, Massachusetts, primarily involving parenteral drug abusers (PDAs) and their sexual contacts. As of August 1, 1984, 75 cases of acute HB have been identified, 50 of which are considered outbreak-related. Fulminant hepatitis has been a prominent feature of this outbreak. Six deaths have occurred, for an outbreak-related case fatality ratio of 12%.

Patients meeting all the following criteria were considered outbreak-related HB cases: (1) an acute clinical illness compatible with HB; (2) elevated serum glutamic-oxaloacetic transaminase (SGOT) or serum glutamic-pyruvic transaminase (SGPT) two or more times greater than the upper limit of normal (when such results were available); (3) positive serology for hepatitis B surface antigen (HBsAg); (4) residence and/or primary diagnosis and treatment within the city of Worcester; and (5) a PDA or a direct contact of a PDA.

Of the 50 outbreak-related case patients, 35 were male. Twenty-nine were white, non-Hispanic; 17 were Hispanic; two were black; and two were of unknown race. Ages ranged from 15 years to 43 years (median 25 years). Forty-three patients used needles; six were sexual contacts of PDAs; and one had direct contact with open wounds of a person with hepatitis. Of the six patients who died, three were male; five were white, non-Hispanic, and one was Hispanic. Ages ranged from 19 years to 34 years of age (median 27 years). Five were PDAs, and one was a sexual contact of a known PDA.

Drugs that were self-injected were primarily heroin and cocaine. No 3,4-methylene diamphetamine (MDA), a drug implicated in fulminant HB/PDA deaths in North Carolina in 1979, was used.[1] The only potential hepatotoxin identified was alcohol.

Testing for HB markers confirmed HB in all cases. Serum specimens were available from four patients who died; three had immunoglobulin M (IgM) anti-delta virus antibodies. IgM anti-delta virus antibodies were also present in four of 22 PDAs with nonfulminant acute HB, one of seven PDA contacts with nonfulminant acute HB, and none of 11 nonoutbreak-related patients with acute HB. In addition, two of 13 non-ill HBsAg-positive PDAs had serologic markers of delta virus infection (one with IgG antibodies and one with IgM).

Editorial Note: Previous clusters of fulminant HB deaths among PDAs have been reported in this country;[1, 2] however, this is the first outbreak of fulminant HB in the United States in which the delta virus has clearly been shown to have contributed to the severity of the illness.

Delta virus is composed of a protein antigen (delta antigen) and a ribonucleic acid of low molecular weight. Although transmissible as an independent infectious agent, delta virus can only infect and cause illness in the presence of active HBV infection. To be infectious, this incomplete virus requires a coat of HBsAg.[3] Delta virus and HBV may simultaneously infect a host (coprimary infection with HBV/delta virus), or delta virus may superinfect an existing HBV carrier. Either coprimary infection or superinfection may cause acute hepatitis; both types of infection have been associated with fulminant HB in Europe.[4]

Delta virus infection is endemic in southern Italy. Based on limited serosurveys, it has also been found in the Middle East and in certain parts of South America and Western Africa. Superinfection with delta virus was implicated as the major cause of an exceptionally severe hepatitis epidemic among Venezuelan Indians in which 34 of 149 patients died.[5] Delta virus infection has been limited to hemophilia patients and PDA populations in the rest of Western Europe, North America, and Australia.[7, 8] Fulminant coprimary HBV/delta virus infections among PDAs have occurred sporadically in Los Angeles.[6]

Although delta virus is transmitted in a manner similar to HBV, to date, delta virus infection has not been reported in this country in health-care workers or male homosexuals, the other major groups at risk for HB. Because delta virus infections have never been found in the absence of infection with HBV, there appears to be little risk of spread outside of groups known to be at risk of acquiring HB. Testing for delta virus is indicated in the setting of fulminant HB infection or acute hepatitis occurring in a known HB carrier.

Control of HB outbreaks among PDAs is difficult. Efforts to control the current outbreak have focused on educating PDAs on the modes of transmission of HB and on updating physicians regarding serodiagnosis and reporting of HB and recommended prophylaxis of needle, sexual, and familial contacts of patients.[9] Since HB vaccine will prevent both HB and delta virus infections, a program to vaccinate PDAs in Worcester is currently under development as a control measure.

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Outbreak of Diarrhea Linked to Dietetic Candies — New Hampshire

A 13-year-old girl was treated at a Milford, New Hampshire, hospital emergency room April 30, 1984, for acute abdominal pain and diarrhea. Induced vomiting yielded partially digested pieces of a hard candy. The New Hampshire Poison Center notified the Epidemiology Office, New Hampshire Division of Public Health Services, that candy possibly caused the illness.

Investigation disclosed that, earlier that day, eight neighborhood playmates, ages 5-13 years (mean 9 years), had experienced abdominal cramps, urgency in defecation, and two to six loose bowel movements each, ½ to 1½ hours after eating three to 16 pieces of a dietetic candy per child. There was no known common exposure to other food, drink, or toxic substance. Only the 13-year old girl received medical attention; the other seven children recovered spontaneously within 2-3 hours after the illness began. Each of three additional playmates who ate one piece of candy and four who ate no candy did not become ill. The attack rate for children who had eaten any of the candy was 8/12 (67%); it was 8/9 (89%) for children who had eaten three or more pieces.

The candies, purchased locally, had been manufactured in Pennsylvania and are one of a number of dietetic candy products distributed widely for the past 6 years to retailers throughout the United States and to countries overseas. The candies in this outbreak each contained approximately 3 grams of sorbitol as a sweetener. Sorbitol, a hexahydric sugar alcohol, acts as an osmotic laxative. The candies were purchased in bulk and individually wrapped. The wrappers carried no ingredient information and no warning of adverse effects if eaten in excess. A survey of a number of sorbitol-containing dietetic products on the market in New Hampshire revealed instances of inadequate and inaccurate labeling.

Editorial Note: Sorbitol has been responsible for both acute and chronic diarrheal illnesses in adults and children.[1-3] In a normal adult, after a 35-gram oral dose, levels of sorbitol in blood remain undetectable, and serum glucose remains unchanged.[4] Ingestion of 10 grams of sorbitol caused bloating and flatulence in most of seven volunteers in one study. Twenty grams caused more severe symptoms of cramping and diarrhea.[5] In children, the dose of sorbitol required to produce gastrointestinal symptoms is markedly less than in adults. Sorbitol ingestion has not been associated with harmful effects other than diarrhea and gastrointestinal discomfort. In unexplained cases of acute or chronic diarrhea, a careful dietary history should be obtained, with careful attention to the possible ingestion of sorbitol.

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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

February 17-20

Improving Residency Rotations: Curriculum Planning and Negotiations
Place: Rougemont
Credit: 20 hours Category I AMA, AAFP
Info: Dr. Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

February 18-20

Selected Topics for the Practicing Clinician
Place: Durham
Credit: 24 hours Category I AMA, AAFP
Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 6

Eating Disorders of Childhood and Adolescence
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-3571

March 7-9

Diving Accident Management and Hyperbaric Oxygen Treatment
Place: Durham
Credit: 20 hours Category 1 AMA; 2.0 CEU
Fee: $280
Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 20

Pulmonary Embolism — Acute Care and Prevention
Place: Sanford
Credit: 2 hours Category 1 AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

April 13

Neurosciences Update
Place: New Bern
Info: William B. Hunt, Jr., M.D., Box 2157, New Bern 28560. 919/633-8607

April 15-June 7

Postgraduate Course in Medical Sonics
Place: Winston-Salem
Credit: 35 hours Category 1 AMA per week
Info: James F. Martin, M.D., Center for Medical Ultrasound, Bowman Gray School of Medicine, Winston-Salem 27103. 919/748-4505

April 17

The Back — From Thoracic to Sacral
Place: Sanford
Credit: 2 hours Category 1 AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

April 25-27

New Expanded Advanced Cardiac Life Support Provider Course
Place: Asheville
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Fee: $300
Info: Daniel L. Dolan, M.D., MAHEC, 501 Biltmore Avenue, Asheville 28801-4686. 704/258-0881

May 1

The Pregnant Therapist
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-3571

OUT OF STATE

February 16-23

Radiology Postgraduate Course
Place: Ixtapa, Mexico
Credit: 25 hours Category I AMA
Info: Jackie Wright, Box 3834, DUMC, Durham 27710. 919/681-2711 ext. 285

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Duke Aging Symposium
Place: Palm Beach Gardens, FL
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Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 4-7

Interventional Techniques and Radiologic Management of the Emergency Patient
Place: Williamsburg, VA
Fee: $425
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 16

Reconstructive Plastic Surgery
Place: Richmond, VA
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 29-31

Ophthalmology: Cataract Surgery and Intraocular Lenses
Place: Williamsburg, VA
Fee: $275
Info: Kay Parrott, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 12-14

Third Annual Symposia on Anesthesia for Ambulatory Surgery
Place: Williamsburg, VA
Fee: $250
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 19-21

Seventh Annual Conference on Emergency Medicine for the Primary Care Physician
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-27

Twentieth Annual Pediatric Springfest
Place: Williamsburg, VA
Fee: $235
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-28
Annual Meeting, Virginia Society of Otolaryngology-Head and Neck Surgery
Place: Irvington, VA
Info: Donna Strawderman, 4205 Dover Road, Richmond, VA 23221. 804/353-2721

May 3-5
Fifth Annual Clinical Concerns in Primary Care
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

May 10-12
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Place: Williamsburg, VA
Fee: $275
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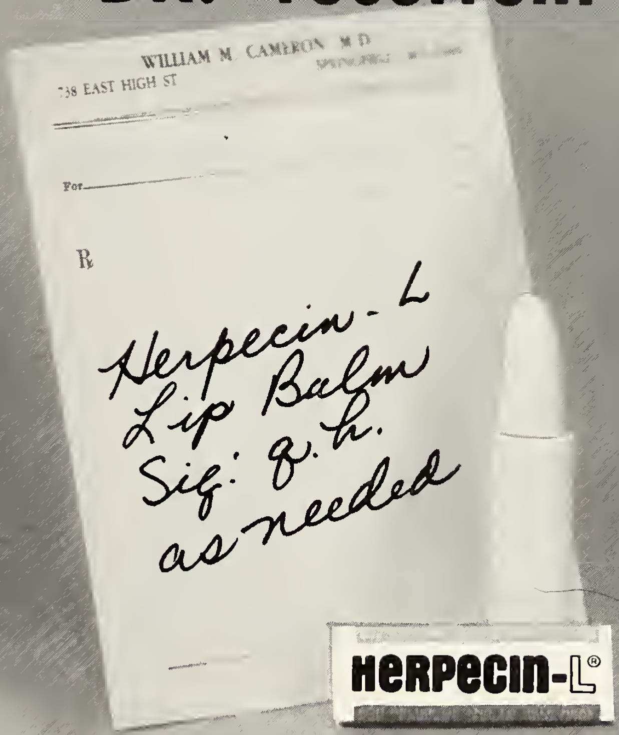

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Letters to the Editor

The following letter was accompanied by a photocopy of the St. Paul Medical Services Division advertisement from page 777 of the December NCMJ.

To the Editor:

This same carrier with such wonderful "commitment" for 50 years pulled out of our state when they were *clearing* hundreds of thousands of dollars.

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If it had not been for N. C. Medical Mutual, many of us would have been left high and dry with no opportunity to obtain any insurance (malpractice), although we had never had any claims.

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H. W. Johnson, M.D.
5305-G Wrightsville Avenue
Wilmington 28403

Panic Disorder

To the Editor:

Dr. Burch's editorial on hypoglycemia[1] is an excellent review of this popular but uncommon disorder and the challenge presented by patients whose complaints suggest this syndrome. The differential diagnosis of patients with symptoms of adrenergic discharge is exhaustive and well known. One of the more recent additions to this list, however, seems to be frequently overlooked by specialists and primary care physicians alike: panic disorder. This psychiatric term for a predominantly biological process is a handle that often fits, and is (best of all) readily responsive to treatment. The following case is a typical one.

A 31-year-old female nurse was referred to the ECU Med/Psych Clinic for evaluation of "shaking spells." For the previous two years she had experienced frequent discrete episodes of various symptoms, including diaphoresis, tremor, nausea, fatigue, weakness, headache, dry mouth, blurred vision, and anxiety. While these episodes were not consistently related to food intake, she nonetheless felt strongly that she was suffering from fluctuations in her blood sugar, and had been evaluated by at least two endocrinologists as well as several other physicians. Physical exams, numerous blood glucose determinations, several glucose tolerance tests, various serum chemistries, and thyroid function tests had all failed to demonstrate any disorder of glucose metabolism or other evident disease. She had also been seen periodically by a psychologist for help in dealing with some situational problems, but had noticed no change in her symptoms during these times.

Panic disorder is defined[2] as an anxiety state manifested by panic attacks ("discrete periods of apprehension and fear" with physical symptoms of adrenergic excess) which occur spontaneously and without apparent precipitants (such as physical exertion, exposure to danger or phobic objects, underlying medical or psychiatric disorders, and the like). It is not uncommon, affecting perhaps 1 to 3% of the population, and occurs most often in young to middle-aged females. While distinct from the agitated distress which frequently results from ruminative worrying ("crescendo anxiety"), spontaneous panic attacks can often result in a secondary or anticipatory anxiety in which the patient avoids those places and situations associated with previous attacks. The pathophysiology for panic disorder is still undefined, although a recent model[3] suggests that changes in intraneuronal pH and lactate levels underlie the physical symptomatology. Drug therapy with tricyclic antidepressants or monoamine oxidase inhibitors usually results in a rapid and marked improvement, as does treatment with alprazolam (Xanax), a triazolo-benzodiazepine with both anti-anxiety and anti-depressant effects.

Since this patient met the criteria for panic disorder, the nature of this syndrome and the possibility that it was her diagnosis were fully discussed with her. Physical exam, serum chemistries, and an overnight dexamethasone suppression test were all within normal limits. Alprazolam, which she had taken on occasion at a bedtime dose of 0.5 mg for sleep, was increased to 1.0 mg t.i.d., and within 10 days her symptoms had abated. She has been maintained on a lower dose for several months without recurrence.

She continues to occasionally see her psychologist for assistance in dealing with the other stresses in her life.

James G. Peden, Jr., M.D.
East Carolina University School of Medicine
Greenville 27834-4354

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Education vs Training

To the Editor:

I think your editorial, "Training Is No Substitute for Education" (NCMJ 1984;40:579-80), was timely and pertinent. It is a message that somebody should remind us of from time to time.

J. Stuart Gaul, Jr., M.D.
1900 Randolph Road
Charlotte 28235

Creation vs. Evolution

To the Editor:

In the August 1984 issue of the *North Carolina Medical Journal* there was an editorial entitled "A View from the National Academy of Sciences: Science and Creationism." This was almost entirely a quotation from Dr. Frank Press as he wrote the preface to a booklet entitled *Science and Creationism* that was written to be distributed by the National Academy of Sciences. After reviewing the editorial I waited through the September, October, and November issues for some response to the statements Dr. Press made. This wait has been in vain as there apparently has been no response or at least none that has thus far found its way into the *North Carolina Medical Journal*.

Since I realize that an evolutionist may experience a dangerous rise in his blood pressure when someone points out the grossly unscientific nature of the evolutionary theory, I hestitated to respond to Dr. Press. However, in the long run I yielded to the urge to take a chance with the blood pressure problem knowing that we can usually treat this particular situation successfully. How I wish the muddled reasoning of the pseudoscientist who believes in evolution could be dealt with as easily.

Dr. Press did not at any time address the essential and all-important question of our origin in the preface to the booklet *Science and Creationism*. Instead just as in the title that the National Academy of Sciences has chosen for the booklet, the statements he made would have one believe the evolutionary theory is a proven fact and that the theory of creation is unscientific. Such is far from the actual truth. Dr. Press says, "Most important, the scientific method requires that the fact-seekers remain open-minded, are willing to accept changes indicated by the signposts of evidence." I could not agree more. However, I have been amazed for years that the evolutionists generally refuse to examine the facts in an open-minded way. If we are to gain anything from examining the theory of evolution as compared to the creationists' theory of our origin, our examination must be ruled by the accepted scientific observations that pertain to the origins of the human species. Fortunately for our discussion there are plenty of facts to peruse.

On the other hand, Dr. Press says, "The theory of evolution has successfully withstood the tests of science many, many times." This is untrue since the evolutionary theory would crumble instantly when compared with the known facts of science.

What are the tests of science? Since Dr. Press does not mention them, allow me to list some of the more important. First, in discussing the origin of species, have we ever seen a single new species develop from a previous species? The answer is in the negative. Which theory does this fact support? Obviously it supports the creation theory.

Secondly, do we have any scientifically acceptable documentation of human life on this planet beyond 10,000 years ago? Again we must give a negative answer, and again we must admit that there being no earlier fossils of humans prior to this rather short length of time, the evolutionary theory again diminishes in scientific importance. It should even be mentioned that some unscrupulous evolutionists in their zeal to supply scientific proof to the theory of evolution have manufactured gigantic hoaxes to prove scientifically their theory when they cannot find support for it otherwise.

Thirdly, does the early existence of animal life many thousands of years ago prove or support the theory of evolution of man from lower animals? Obviously, it does not unless some type of bridge between the two is also evident. There being no evidence of such a bridge the mere existence of animal life a million years ago does not bear at all on a theory of evolution of the human species.

Finally, what does the fact that evolutionists will not respond to the above questions and similar facts relative to our origin say about the strength of their scientific basis? Obviously when one side of a supposedly scientific discussion will not address the observable facts as Dr. Press has recommended, it certainly denegrates his stand in the eyes of the scientific world. We should watch very carefully and see which side of the debate accepts the observable facts open-mindedly and which side does not. Evolutionists constantly seek to persuade and convince by prejudice and deceit. Such can never be considered as scientific evidence.

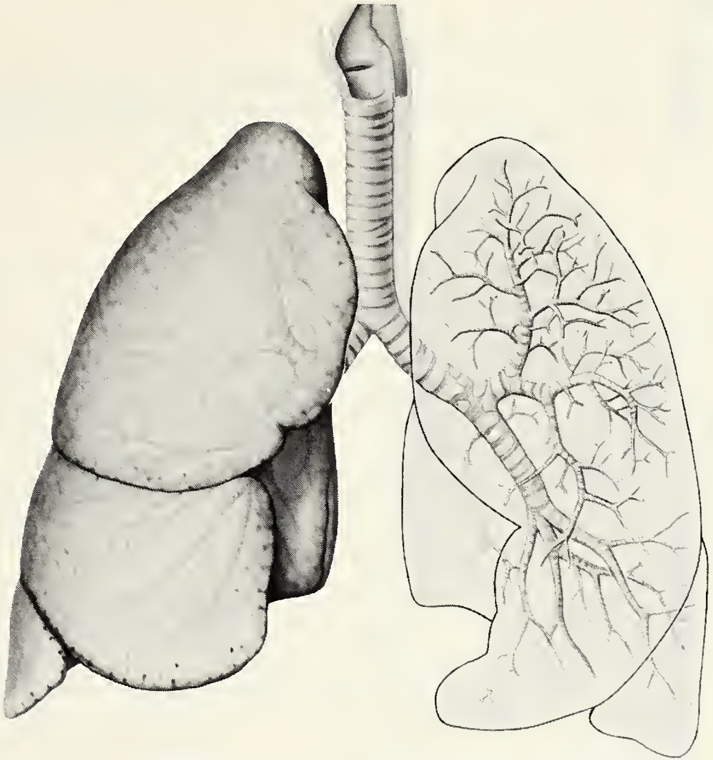
Dr. Press points out the fact that we once thought the world was flat. Also at one time the majority of people looked upon earth as the center of everything, when now we know the earth is not even the center of our little solar system. Consensus changes but truth does not.

Other things regarding science could be said, and I for one applaud any effort of science to examine this issue in a scientific way. If purely scientific views had been used to examine our origin, there would not be much to talk about now. Unfortunately the theories of origins are involved, like it or not, with one's understanding of God. Since this is true, preconceptions have been and continue to be very influential in everyone's considerations regarding how man arrived here. Dr. Press recognized this fact when he said that acceptance of the evolutionary theory does not alter the religious principles of many religious leaders. I must agree with Dr. Press on that statement. However, I will remind you that even though we have many excellent religious leaders, it was the religious leaders who led the crusades, held the inquisitions, allowed pogroms in many areas, and caused our Lord to be crucified. This debate is hardly a place to appeal to support from "religious leaders." Instead I believe that only scientific evidence should be admissible.

The truth is that despite the various similarities between man and lower animals, we have certain irreconcilable differences. Dr. Michael DeBakey recently pointed out the major biological species barrier between man and animals in discussing the transplantation of animal hearts into man. Man and animals have no common ancestry. The greatest of these differences is not our chromosome count or adult physiognomy which of course is enough to disprove the theory of evolution to the true scientist with an open mind. The difference of which I speak is the matter of the eternal soul. This subject is the only consideration I know where consensus favors the creationists, because most people believe man is a spirit who possesses an eternal soul. This is very strong among Jews and Christians and has been shown by many surveys to be a majority opinion in this country. Only the creationist has a reasonable explanation for this as the evolutionist is generally convinced that man is simply a higher animal and has no intrinsic spiritual difference from lower animals. If one wishes to deny humankind's eternal considerations and overlook the many scientific facts of the matter of man's origin, then and only then can he take the ultimate in scientific hypocrisy and support the incredible theory of evolution.

Marion W. Griffin, M.D.
127 McArthur Street
Asheboro 27203

Consider the causative organisms...



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Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* Other causes of colitis should be ruled out

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy — Pregnancy Category B — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note. Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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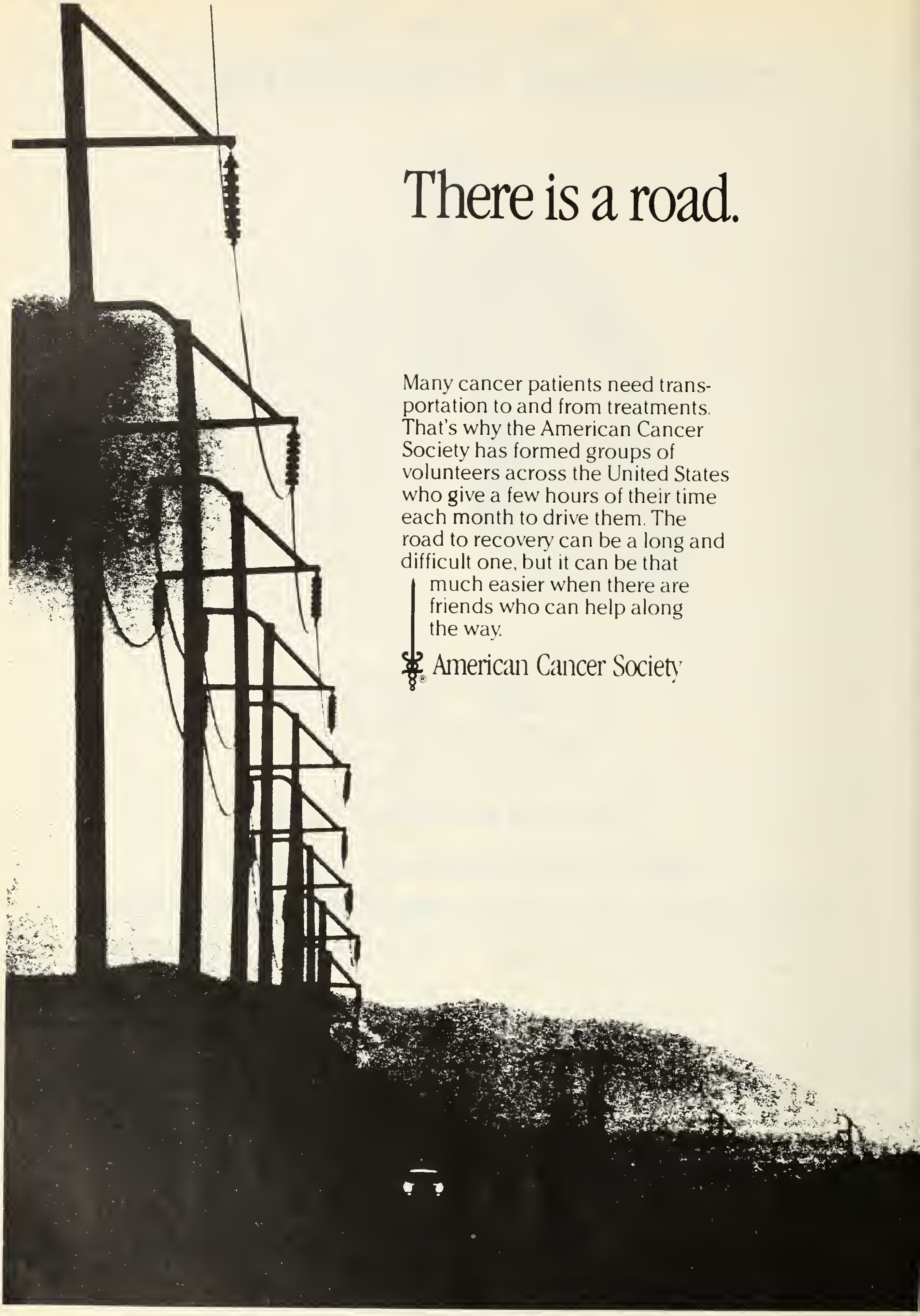

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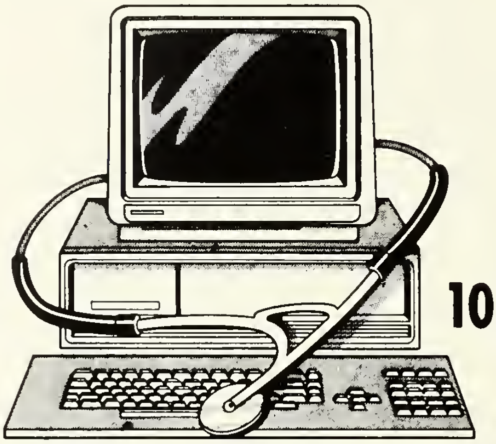

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SPECIAL ARTICLE

Medical Economics, Ethics, and Education: Some Old Wines in New Bottles

Milton W. Hamolsky, M.D.

I am honored by your invitation to serve as your Sergei Zlinkoff Visiting Professor for 1984. I participated, as a medical resident under Dr. Hermann Blumgart at the Beth Israel Hospital in Boston, in the medical care of Mr. Zlinkoff when he was referred from New York for further study and attempted management of his complex, difficult, and unresolved medical problems. His private physician was Dr. Mack Lipkin, unknown to me but described by Dr. Blumgart as the "finest practicing internist" he knew. We failed to make any substantive contribution to Dr. Lipkin's understanding or plan of management for Mr. Zlinkoff. I learned more, and probably for the first time, about the realities of "the art" of medicine and the limitations of "the science" of medicine from Dr. Lipkin who became, and has remained, my prototypic role model of the knowledgeable, experienced, wise, and caring patient's doctor and teacher of students. Despite, but also partly because of, our frustrations, Mr. Zlinkoff willed a large sum of money — in tribute to Dr. Lipkin — for the creation of a Foundation for Medical Research and Education. Two years ago, the Board of Trustees of that Foundation — again in tribute to Dr. Lipkin — created five Visiting Professorships to foster the principles exemplified by Mack at five medical centers where Dr. Lipkin had made his unique mark. I am proud but humbled by this opportunity to add my personal and professional tribute to Dr. Mack Lipkin.

When I received your invitation, visions of sweeping and profound and statesmanlike pronouncements on the great issues of Medicine flitted kaleidoscopically through my mind. At last — the opportunity to address to a captive audience such problems as the Growing Crisis in Medicine; the Decline of the Physician in Society; the Impact of the Scientific and Technological Explosions on the Humanism of Medicine; the Science versus the Art of Medicine; Specialization, Fragmentation, Non-accessibility within the Medical Care System; the Soaring Costs of Medical Care and the Demands by Government, Business, Insurers, and the Public to Contain Costs while Assuring High Quality of Care for Every Citizen; the Rising Roles of the Government, the Consumer, Third Party Payors and an Avalanche of Alphabetized Regulatory Agencies; the Law and Ethics and Politics in Abortion, Death with Dignity, Research on Humans, Do Not Resuscitate Policies, Allocation of Limited Resources, Rationing of Health Care, Medicine's Share of the GNP, etc. — ad infinitum, ad absurdum, and ad boredom. And then, as is the special privilege of the outside consultant, to leave town before you have figured out what he really said.

My surging "ego," however, was flattened by my more realistic "id" — for I do not consider myself particularly qualified to bring to this medical center any unique insights which have not already been offered profusely by Medicine's more qualified statesmen. I would be more comfortable sharing with you some experiences in my personal intellectual hobby of Endocrinology — and the thyroid in particular. But that is not, in my understanding, the purpose of the Zlinkoff Professorship. I have chosen, therefore, to offer some personal reflections on biases based on the experiences I have been privileged to enjoy as a clinician, teacher, one-time academic researcher, and administrator of sorts.

A favorite ploy of the lecturer to reawaken his audience is to quote some trenchant pronouncement and then emphasize its timeless relevance by revealing that it was written in, say, 1895. Let me offer such a quotation:

"My basic thesis is that the fundamental strength of medicine has been, is now, and will always be the one-to-one highly personalized relationship of a patient and his/her doctor — the individual human being in pain or anxiety or fear and the chosen doctor dedicated to cure the disease if possible, if not . . . to alleviate the pain or suffering and, in any event, to share and ease the discomfort of body and mind. When all the smoke of rhetoric has cleared — of politics and economics and philosophy — and when the threatening promise of the computer has reached its equilibrium — that interpersonal relationship will remain the final common pathway of the nobility of medicine. And I submit that it is the slippage of that noble tradition which is the root of most societal disaffection, of the malpractice crisis, of the increasing interpositions of others between the patient and the doctor, of the growing threat of governmental interventions, of the underlying unease of the patient and the doctor in our society."

Those sentiments, articulated frequently by many, were offered by me just seven years ago in an address to one of the first graduating classes of the new Brown Medical School. I believed them deeply. I want to believe them now. But I wonder about the recent forecast by the physician chairman of the American Hospital Association Council on Physicians. "I see," he states, "only two kinds of doctors surviving (in the future) — those who are affiliated

---

Dr. Hamolsky presented this lecture at the University of North Carolina, Chapel Hill, October 18, 1984 as the second Sergei Zlinkoff Visiting Professorship Lecture. Dr. Hamolsky is Professor of Medical Science, Brown University, Providence, RI.

with alternative provider systems and those who are directly affiliated as hospital staff physicians. This means the end of the voluntary medical staff as we know it. Hospitals will no longer be able to afford (sic!) the individual solo practitioner who has no vested interest in the preservation of hospital resources through cost-effective medical care and is unlikely to control a sufficient volume of admissions to have the leverage over hospital administration that they have had in the past.'' I have difficulty grasping any substantive link in that bleak outlook to the Care of a Patient concept of Francis Peabody or Hermann Blumgart.

To retain some semblance of my ingrained concept of Medical Grand Rounds, I would begin with the case history of Mrs. A. G. — a 78-year-old housewife, mother of three children, who entered our hospital because of her second — or perhaps third — stroke. She was unresponsive on entry and bits of her history were garnered from a daughter, her recently engaged rheumatologist, and her hospital record.

Mrs. G. was characterized in her early years as a strong, active, intelligent, self-sufficient wife and mother, who had been for the last few years in her usual state of chronic, debilitating, deforming arthritis for which she was receiving Prednisone but caring for her progressively senile and incapacitated 82-year old husband, despite one or two strokes which had left her with residual left-sided weakness and some slurring of speech.

She also had hypertension and was on two antihypertensive agents, adult onset diabetes mellitus, moderately well-controlled by an oral antidiabetic agent, a history of angina pectoris with, possibly, one major ischemic episode two years previously, mild congestive failure treated by digitoxin and Lasix, and mild azotemia (serum creatinine of 2.8). She was also taking Elavil because of some depression over the past one to two years.

Evaluation in our Emergency Department revealed a comatose patient responding only to painful stimuli, blood pressure of 180/112, pulse of 118, 32 respirations, and temperature of 102°, left-sided paresis, and right-sided paralysis, slight neck stiffness, distended neck veins, bilateral basilar rales, 2+ peripheral edema, multiple premature beats (by EKG, multifocal ventricular contractions), depressed reflexes with a positive Babinski reflex on the right, unequal pupils, nonpalpable arterial pulses distal to the femorals. Studies revealed an elevated WBC with a shift to the left, mild anemia, blood sugar of 283 with 2+ acetonuria and 2+ proteinuria, serum creatinine of 3.6, normal electrolytes except for a serum potassium of 3.1, mild hypoxemia with CO_2 retention. Normal values were obtained for the sedimentation rate, prothrombin time, partial thromboplastin time, uric acid, serum bilirubin, serum calcium, and phosphorus, total protein and A/G ratio, SGOT, LDH, creatinine kinase, serum amylase and alkaline phosphatase. EKG revealed Q waves in leads 2, 3, and AVF. Chest x-ray revealed an enlarged heart with bilateral congestion and a questionable area of beginning consolidation in the right lower lobe. A CAT scan was unrevealing except for moderate cerebral atrophy; EEG revealed a diffuse metabolic encephalopathy. Lumbar puncture revealed elevated pressure and protein and 450 red cells per $mm.^3$

She was treated with oxygen, Lasix, Ampicillin, regular insulin, hydrocortisone and a slow I.V. drip for keep-open purposes. Shortly after entry, she developed ventricular tachycardia which responded ultimately to Procainamide but was followed by hypotension which responded to Dopamine. Because of progressive CO_2 retention, she was intubated and transferred to the Intensive Care Unit. Despite all measures, she remained comatose but was sustained on a respirator, monitor, and I.V. hydration. Several runs of ventricular tachycardia were managed pharmacologically. Her EEG deteriorated but continued to show scattered, sporadic spikes. The neurologist declared her status as essentially irreversible.

After ten days on the Intensive Care Unit, her ventricular ectopy gradually subsided, her blood sugar, electrolytes and blood gases were normalized, her blood pressure was controlled at 150/94, her creatinine stabilized at 3.2, a urinary E. coli infection and her presumed pneumonitis responded to antibiotics and she was transferred to the Medical Ward, essentially stable but comatose.

The resident and nursing staffs continued their exemplary clinical care. One daughter requested that ''everything possible be done for mother.'' Another daughter and son revealed that mother had once stated, ''If I ever become like poppa, please do not let them keep me alive with all those tubes.'' Her rheumatologist, the physician-of-record, had only recently undertaken her care, for her old family doctor had died. He advised continuation of all therapies, was unwilling to write a DNR order but advised that, if she failed, a ''slow-code'' should be carried out. The Utilization Review Committee advised the physician that she had received the maximum allowable hospital care and attempts were undertaken to transfer her to a long-term care facility. The DRG monitor advised us that Mrs. G. had passed into the ''outlier'' group. After 47 days, her blood pressure dropped progressively despite Dopamine, and she expired.

Her hospital bill was $73,000.

What can we learn from such an experience? I would offer some selective personal reflections — under the rubrics of economics, ethics, and education.

A growing body of anecdotal experiences, retrospective data, and ominous projections indicate that the problems of Mrs. G. will increasingly dominate the medical scene. The progressive aging of our population is now a given — much of it the inevitable result of the advances in medical science, technology, and public health. Our future is enveloped in the constellation of chronically dependent patients; higher costs; the schizophrenia of the health care planners in sober and detached objectivity versus the family and patient in the Emergency Department and Intensive Care Units who want the very best — now; the political platitudes of one class, high quality care for all versus the hard, increasingly dominant finality of those who pay and, therefore, call the tune; the cool rationality of the — uninvolved — philosophers, humanists, and ethicists except when they or family are patients; the lonely physician torn between his primary obligation to his patient versus his societal responsibilities to the larger community.

The litany of medical economics is impressively persuasive. Rising hospital costs, increasingly expensive technologies, ancillary services, drugs, long-delayed improvements in salaries of health care personnel, the general economic stagnation and inflation of the 70s, over-supply of hospital beds, the putative physicians' glut, escalating annual costs for business of employees' health benefits, a tottering Medicare system threatening an already endangered Social Security system, etc., have contributed to the oft-repeated — and increasingly accepted — dogma that society has decided that Medicine's 10 to 10.5 percent share of the GNP is "enough." In the economists' view, according to Fuchs, 1) resources are scarce relative to wants, 2) these resources have alternative uses, and 3) people have different wants and assign different values to them. The economists' problem is how to allocate resources optimally to meet health needs. And so we have spawned prospective rate setting, certificates of need, maxicaps, zero budgeting, reallocation of resources (euphemism for whose ox gets gored), Health Planning Councils, a national center for technology assessment (which lasted only three years), increasingly raucous debates over "competition" versus "regulation," HMOs, PSROs (now PROs), DRGs, redesigned benefit packages (copayments and deductibles), pre-admission certification, utilization review, mandatory ambulatory surgery, mandatory second opinions, home care programs, use of alternative delivery systems, preferred provider agreements, the "prudent-buyer" concept, health care coalitions, for-profit health care systems, hospice programs.

Somehow, the case of Mrs. G. is overwhelmed by this statistical deluge. Yet it is symbolic. Can Medicine justify the growing thousands of Mrs. G.'s and the do-everything-we-can approach for all? To what end?

I am impressed that there is "fat" in the system. Every serious attempt to validate the use of lab tests and ancillary diagnostic procedures results in a 20% reduction — at least while the supervision persists. Various prepayment plans do appear to result in significantly lower hospitalization rates. The growing challenge to the "do everything we can" approach to the Mrs. G.'s is valid and gaining adherents. I am concerned, however, over the growing power and dominance of the "cost containment" component of the equation. I believe that Medicine's greatest challenge in this sphere is to effect a more realistic balance of the usually coupled — but usually submerged — component of the quality of care. It is far easier to calculate costs, to dominate with impressive charts and graphs. Although we profess to know quality, we have failed to present our case with comparably impelling force. We have failed to define reasonable limits, we offer insufficient countervailing quantitative economics of the values and quality of the life we prolong, the technologies we offer, the benefit component of the cost/benefit ratio. Pioneering efforts are now being made — chiefly by the newly evolving Divisions of Primary Care or General Internal Medicine. They merit our strong and sustained support. For we must be constant participants in the ongoing dialogues of allocation of health-care resources, and we must have data and reasonable plans and feasible operations. Otherwise our past platforms of medical research and medical education will be undernourished and the result will be an inevitable deterioration of the health care we will be able to provide.

Some personal examples come to mind. I believe that when I was a resident I, too, would have "done everything" for Mrs. G. For I knew that it was not my privilege to play God; I knew that failure to do everything I could bordered on the unacceptable euthanasia; I was more comfortable in doing something rather than the more ego-threatening, carefully valued, selective procrastination; it was easier to impose my previously nurtured dedication to treat, to cure, to save than to grapple with the bothersome considerations of family members or — even more unsettling — the vaguely indistinct or clear, but suspect, intimations of the dying patient. But now, after 30 years of personal experiences (most of which were unique lessons which, somehow, did not solve the next one) and learning from the changing values and expectations of our society from the pronouncements of the humanists, economists, ethicists, and politicians, I am not so sure. I am now more prepared to stay my hand — to explore the patients' preferences, to adjust to the families' concerns (for I have learned that many — perhaps most — families are grateful to the physician who will open and lead the discussion of alternatives, alleviating their guilt to be the initiators).

In a recent two-week period, I counted eight articles in the *New York Times* on "Many See Mercy in Ending Empty Lives," "The Courage to Talk About Death," "French Doctors Admit Helping Patients Die," "A Person Owns Himself," "The Struggle to Save a Life Already Lost," "Declaration on Euthanasia of the Vatican," "Bureaucracy Should Not Intrude," "One-Sided Dialogues (the Failure of Physicians to Discuss the Issues of CPR with Patients and Their Families)."

I am not significantly more certain of what is *the* right course in so many cases of Mrs. G., but I am more secure in my responsibility to consider assuring comfort and accepting DNR and, if that is the careful consensus, to write the explicit orders and the explanatory progress note, to withhold the respirator, feeding gastrostomy, cardiac pacemaker, to do without the sedimentation rate, serum bilirubin, multiple blood gases and electrolytes, alkaline phosphatase.

Another personal reflection — as chief of a Department of Medicine, I receive from our administration a monthly, computerized print-out of the performance of each member of our medical staff — compared with our hospital-wide averages — listing each individual patient of the physician, his DRG classification, the length of stay, use (and cost) of x-rays, lab tests and other ancillaries and, most pointedly, the total cost of the stay to the hospital compared with the DRG-Medicare reimbursement. Despite my determination not to be carried along, I find myself focussing on "the losers" as compared with "the winners." I do not know what the ultimate impact — local or Federal — will be, but I am uneasy. I have heard of two orthopedists in another hospital whose staff reappointments were denied because their lengths of stay for hip and back cases were 21% above the median of other staff orthopedists. Their suit is now in the courts. I have heard rumors of modification or elimination of the reimbursement for medical education costs of residents and fellows. And I am uneasy.

I reflect also on the inordinate costs of malpractice insurance. Impressed by the general thrust for fair and equitable settlements in cases under the Workmen's Compensation

Act in our community as compared with the a priori imposition of an adversary battle to prove malpractice by someone or anyone when a patient has suffered an adverse or unexpected outcome, I suggested to our Medical Society and legislative representatives creation of a new system fashioned after the Workmen's Compensation mechanism. I was commended for my civic zeal and then gently squelched for my naivete with the admonition that 92% of the State legislators are lawyers. ''Do you really think,'' I was asked, ''that they will ever vote for such a change?''

There is another paradox of medical economics, less honorable in its ethical implications but increasingly more real in my experience. Society, or its spokespersons, proclaims its preference for the ''good old family doctor type of M.D.''; its vocal spokespersons decry the lack of preventive medicine, holistic care, and the generalist. But society's mechanisms for reimbursement deny the resultant logical resource allocation. Society pays well for the hospitalized patient, for surgical procedures, for the specialist with his invasive technologies, for the performance of all kinds of lab testing. But it does not recognize the physician who spends the extra time to communicate more fully with his patient and family, society will not stop smoking, nor wear seat belts, nor consume less alcohol, nor reduce overweight, will not reimburse appropriately for many elements of ambulatory or preventive care. Quality physicians on my staff have convinced me that they are sensitive to the importance of, and need to, communicate more fully with their patients, but that they are frustrated by economic necessities to compromise, that there has been a steady erosion of the personal and professional fulfillments of being a doctor, that there is, simply, not as much fun in being a doctor. Virtually every intern on my staff is deeply in debt when he starts, facing three to five or six more years of training, and then — at age 30 — will face a significant startup cost of building a practice, accelerating malpractice insurance premiums, the looming glut of physicians, difficulties in obtaining staff membership, the realization (as others) of children to educate and the chilling fact that his postponed economic security depends largely on his continuing health and ability to see patients. Since physicians are also human beings, it is unrealistic to ignore the conflicting pressures of society's expectations (and the good physicians' preference) for effective and time-consuming communications on the one hand but a distorted reimbursement system on the other which preferentially rewards hospitalization, acute care, invasive technology, ''doing rather than thinking and discussing.''

I have the uneasy sense that it may already be too late to slow, to modulate the rapidly accelerating juggernaut of the ''economic facts of life'' which daily dominate our local scene and loom threateningly more decisive on the national scene.

The power of the purse is casting a lengthening and enveloping shadow over the doctor's traditional prime obligation to his patient, insinuating its determinative role upon our ethical standards of professional conduct. I received two weeks ago the Ethics Manual of the American College of Physicians, reprinted from two 1984 issues of the *Annals of Internal Medicine*. The table of contents lists some 36 topics such as the Physician-Patient Relationship, Financial Arrangements, Informed Consent, Conflicts of Interest, Sharing Fees, The Incompetent Colleague, Advertising, Obligations of the Physician to Society, the Relationship of the Physician to Government, to the News Media, to other Health Professionals, Commercialization of Medicine, Physician Unions and Strikes by Physicians, Resource Allocation, Medicine and the Law and, finally, Patient Autonomy, Quality of Life, Care of the Hopelessly Ill. As I read the sections, my thoughts returned to Mrs. G. who symbolizes the awesome dilemmas created by the capacity of modern biomedical technology to prolong and sustain key physiological functions, for indeterminate periods, in patients in vegetative or comatose states balanced uncertainly against increasing public awareness of Medicine's technological virtuosities but prognostic uncertainties, financial and emotional drains on patients and families, emerging patients' rights and patient autonomy and newly evolving concepts of the quality of the sustained biological existence in terms of sentient or cognitive functional potential. Mrs. G. nags at me as I read increasing empirical and retrospective data that the terminally ill receive proportionately much more expensive medical care than other patients, that over 20 percent of all nonpsychiatric hospital and nursing home expenditures are spent on the care of the terminally ill, that although only five percent of all Medicare enrollees died in 1967 and 1968, 22 percent of all reimbursements from that program were made on their behalf, that the cost of care of non-survivors of cancer or intensive care units is roughly twice that of survivors, that intensive care costs seem to be inversely related to the probability of patient survival. Mrs. G. looms before me when I am advised that efforts directed at reducing cost and increasing efficiency must be focused on such high-risk, high-cost, low-yield groups. Yet I am impressed by one cautioning study of intensive care patients that found that ''among non-survivors, the highest charges were due to caring for patients who were perceived at the time of admission as having the greatest chance of recovery and among survivors, the highest charges were incurred by those thought to have the least chance of recovery,'' i.e., patients with unexpected outcomes — death or survival — incurred the greatest costs. The study concludes that ''simple cost-saving solutions, such as withholding resources from the hopelessly ill, are difficult to apply to an individual patient because prognosis is uncertain.'' I am not very comforted by the reassurance of one hospital's Optimum Care Committee that ''economic considerations must never serve as the *sole* criterion for disposition of patients.'' I worry about a vague feeling of the dwindling sanctity of life, so precious a fundament of our profession in the face of the insidious interpolations of cost containment. And yet I struggle to justify my ultimate personal decision to permit and to help Mrs. G. to die with dignity as my primary ethical obligation to do what is best for Mrs. G., unswayed by diverting considerations of economics. Mrs. G. thus symbolizes what I believe will be a growing problem for the caring physician — epitomized elliptically by the conflicting construct of economics versus ethics.

What, then, is the balancing role of medical education? I do not have to certify the glorious accomplishments of science and medicine, the legacy of relief and comfort provided to billions of people on this planet, the primacy of basic scientific knowledge as the lasting foundation of our profession. Somewhere between 1910 and 1912 in this country, it is stated, a random patient with a random disease consulting a doctor chosen at random had for the first time in the history of mankind a better than 50-50 chance of profiting from the encounter. But, we are told, the science of medicine has so dominated our profession that we have come to neglect the patient as a person. The patient, it is said, knows how he feels but doesn't know what he's got, while the doctor knows what he's got but doesn't know how he feels. The milk of human kindness has been curdled by molecular biology. And so the cry is raised from all quarters for a return to "humanistic medicine" — to me a logically redundant tautology. A concept has grown that there is somehow an inherent contradiction between science and humanity, between technology and compassion.

And so we talk of the art of medicine — the unique application of our scientific knowledge and clinical skills toward our primary responsibility to strive to understand the individual human being for the maintenance of health or the amelioration of disease. And we extol the artist in medicine who weaves into his fabric elements of history, religion, sociology, anthropology, psychology, music, art, and literature. There is an important caveat against the growing tendency of some — under the guise of humanistic compassion — to become impatient with the demanding and difficult and everchanging complexities of biochemistry and molecular biology and the hard, long-term attainment of clinical expertise. For compassion and empathy and sharing will not suffice if the physician does not determine that the situational depression of the recent widow is due *this* time to mild hypothyroidism which, once suspected, can be readily diagnosed and cured for a few pennies a day; if he is not alert to the possibility by minimal neurologic changes that the recent migraine headaches which have always, as now, occurred under stress signal *this* time a brain tumor; if he fails to palpate, on *this* visit, an enlarged spleen which might uncover an emerging leukemia in his tired and run-down, always complaining, neurotic housewife or businessman.

I mentioned previously the nostalgic longing for the "good old family doc." I believe that people do not really want the old family doctor with his limited therapeutic armamentarium but are expressing a preference for the doctor who "will take care of me as an individual, who knows (because he cares) about my family background and past history and me as a person, who will listen to me, talk to me, explain to me, give me the knowledge and opportunity to share in my decision-making and health care and not just send me around for a lot of blood tests and x-rays. But he should also know the latest and the best in diagnosis and therapy, or be ready to obtain the best for me when I'm really sick — but still remain the responsible integrator of my total overall care."

As in the schizophrenic praise and blame of science and technology for the blessings and evils for mankind, there is a swelling tide of criticism of medical education for most or all of the decline of humanistic medicine in the modern age. Out of the cascade of papers, lectures, seminars, curriculum committees, task forces and commissions, I have discerned among the pathogenetic mechanisms catalogued 1) a basic genetic imprinting on the RNA and DNA of the doctor-to-be, 2) any or all features of the educational systems before medical school, 3) fundamental changes in society from the basic religious, moral and ethical values of humanitarian and societal concerns to the secular goals of permissiveness, relative affluence, self-fulfillment and personal happiness, 4) the grinding competitiveness to get into medical school, 5) the hypocritical selection process which urges a liberal education in the humanities, social sciences, and arts, but awards the cherished admission largely to science majors with high scholastic grades and skills in mastering the multiple-choice regurgitation of memorized facts, 6) the hardening process of professionalization upon the idealistic medical student who learns to "go along" in order to "get along" in the system, 7) perversion of the medical faculty whose primary role should be to teach but whose reward system is the research productivity priority of the promotion committee, 8) the irresistible pressures toward specialization by peer cloning and economic inequities.

This past month the Association of American Medical Colleges published a pamphlet — *Physicians for the Twenty-First Century* — the conclusions, recommendations, and observations of the Panel created in 1981 on the General Professional Education of the Physician (GPEP) and College Preparation for Medicine. It is a most impressive document, representing the distillation of the thinking and work of representatives of 96 U.S. and Canadian medical schools, colleges, and universities, and professional societies of Medicine. Based on the assumption that all physicians, regardless of specialty, require a common foundation of knowledge, skills, values, and attitudes, it offers five major conclusions, 4-6 specific recommendations relevant for each, the observations leading to the conclusions, an epilogue of Other Important Considerations, an afterword and appendices.

In the Introduction, the Chairman writes, "The medical course cannot produce a physician. It can only provide the opportunities for a student to secure an elementary knowledge of the medical sciences and their applications to health problems, a training in the methods and spirit of scientific inquiry, and the inspiration and point of view which come from association with those who are devoting themselves to education, research, and practice. Medicine must be learned by the student, for only a fraction of it can be taught by the faculty. The latter makes the essential contributions of guidance, inspiration, and leadership in learning. The student and the teacher, not the curriculum, are crucial elements in the educational program." Ironically and somewhat wistfully, this quotation is from the report of a Commission on Medical Education of the Association of American Medical Colleges submitted 52 years previously, in 1932. "Plus ca change. . . . "

It is not possible to encompass with any brevity the sweeping, scholarly, and trenchant pronouncements of this GPEP Report. I recommend its careful study.

I have learned in Medicine, however, that when we are grappling with multiple pathogenetic mechanisms for any disease, it usually means that 1) we do not know the actual mechanism(s), 2) it is difficult to devise a rational therapy, and 3) if our efforts appear to help, we cannot define any responsible cause-and-effect. But, as in all human endeavor, lack of understanding elicits flexible vocabulary, and so we have "idiopathic" or "multifactorial."

I would offer some personal reflections on certain factors in medical education which have impressed me.

Until our genetic probes can pinpoint the chromosomal loci for empathy and compassion, I believe it is possible to teach and to learn those elements subserved by the phrase "humanistic medicine." I have been impressed by the idealism of medical students and later of interns, and by the selfless and humane behavior of many hard-working, dedicated practicing or full-time physicians. I believe I have seen multiple examples of major alterations in sensitivity to, and caring for, people — usually attributable in my judgment to the examples of respected role models. I know — when I reflect — the important shaping of whatever I have become by Dr. and Professor Hermann Blumgart, by Dr. Mack Lipkin, by my chief resident, by my nurse — wife — and by my uncle — an L.M.D. in a small, western Massachusetts town. It is dismaying, therefore, to read the critical assessment by sociologists who followed a class of 80 students from the admission process over three years at McMaster School of Medicine during its determined and massive efforts to correct the cited faults of medical education. They conclude that the progressive loss of idealism of the medical student is not a temporary diversion but rather is inherent in the very demands of professionalization. In their need to strive for competence and passage, students turn off their emotional reactions; psychosocial issues are relegated to secondary importance. They perceive instead the medical profession's expectations of affective neutrality toward patients. The authors describe the loss of idealism in the context of a symbolic moral drama wherein professionalization is seen as a process of differentiation and alienation from lay society and of elevation to a position of detachment and control. The neuropeptides of my gastrointestinal tract rebel against those of my cerebrum but the challenge is clear.

At a more simplistic level, I am critical of the traditional system which greets the student on entry to medical school who comes with an idealism based largely on the anticipation of helping sick or troubled people and, instead, proscribes any meaningful contacts for the eager novitiate with patients for two years, insisting instead on the passive memorization of bones, the brachial plexus, cranial nerves, the Krebs cycle, E. coli, the Fick principle — with a rare, grudging intimation that somehow, some day, it will help the survivors deal with human ills. Is there any wonder that the third year has been viewed as liberation from irrelevant science and, with stethoscope draped insouciantly around his neck, the student is a pushover for the clinician who says "never mind that biochemical junk you had. I'll show you the real stuff." I have seen the intellectual excitement first aroused when the student sees a 23-year-old mother of two who is going blind, relentlessly, from her diabetes because we do not know how to prevent or reverse it and then hungers for the first time to learn carbohydrate metabolism, insulin action, glucagon, membrane permeability, sorbitol. I have seen the interactive excitement of a clinico-pharmacologic or clinico-physiologic session obliterating by the focus on a human patient the artificial barriers between detached basic sciences and clinical relevance by shuttling back and forth around the patient in the same time-frame. I have seen the medical student pursuing in enraptured detail the pathology, biochemistry, physiology, immunology, and psychosociology of his puzzling patient with cirrhosis of the liver. I have shared the maturing efforts of the student when he is first challenged to understand both the disease — the deviation from normal — and the illness, the sum total of the effects of multiple complex factors on his unique human being. I have seen his hurt when he first learns of our limitations in ultimate understanding of most problems, his discomfort when he must make decisions with inadequate data, his pain when he must face suffering he cannot alleviate, or the inevitable failure — to his conditioned psyche — of the death of his patient. These are the essence of medical education — and they require a more appropriate balance of nurturing of the clinical relevance of our scientific knowledge.

Such sentiments have been enunciated more elegantly, eloquently, and forcefully by Professor Neame, a senior lecturer in human physiology at the University of Newcastle in Australia in the September 1984 issue of the *Journal of Medical Education,* supplemented by an accompanying editorial by Dr. Cavazos, a member of its editorial board. Professor Neame presents, in spare and forceful analyses, the most unrelenting, powerful criticism of the non-integration, indeed anti-integration, of basic science to any clinical relevance of the current system of medical school education, defines sharply more proper goals and objectives and offers specific remedies. I urge all of us involved in and troubled by the medical education of our future physicians to read and ponder and react to his landmark contribution.

My experiences lead me to urge the restructuring of our system to elevate the stature, participation, and respect of the experienced, knowledgeable and caring clinician to the a priori guaranteed status of the white-coated, specialized, full-time, research oriented assistant professor.

I hasten to defend myself against the inevitable, reflex attack on such an anti-academic stance. No one respects more than I do the overwhelming values of research, the attainment of peer approval by obtaining competitive grant support, broadening service on National Committees and Advisory Councils, sharpening of critical capacities by service on editorial boards. No one accepts with any more certainty than I do the fundamental and essential contributions of the dedicated army of researchers — basic scientists and clinical investigators — whose collective contributions are responsible for the current and unlimited future status and potential of our noble profession.

But I have learned that all skilled researchers are not a priori effective teachers of medical students. I ask only for a more equitable balance.

One important element of this balanced restructuring relates to the incentive and reward systems for our medical faculties on the campus and in the hospital. Over the years I have heard the pronouncements of the power structure extolling the essential role of teaching and the good clinical teacher in the medical school. But I have been frustrated — as a student when we lost our two best teachers because, we were told, they had not published enough; as a resident when our best practicing clinicians were replaced as Visits by the newest subspecialists, skilled in their restricted spheres but impatient and uncomfortable when challenged by more general problems of our patients; and as a Professor and Chief of a Medical Service when the decisions of our Promotions Committee appeared to take the teaching commitments and skills of our staff faculty for granted, and assigned higher and sometimes final determinative priority to the bulk of publications, or success in obtaining research grants.

My plea again is not for the slightest diminution of the stature of, and sustained support for, the research scientist or research-oriented clinician. I am unreservedly committed to increased and sustained support for basic science and clinical investigation and I decry the short-sighted, short-term vagaries and constrictions of society's support for research. In the context of this discussion, I emphasize the need to upgrade the recognition of and support for the clinical teacher, whether private practitioner or full-time academician, if we really mean what we say about the all-important values of clinical teaching.

In this context also I am increasingly impressed by the fundamental contributions — in the continuing total care of patients, in teaching these relevant basic values, in extending the parameters of research studies — of the newly emerging General Internal Medicine faculty, both those committed to a ''full-time'' academic career and those practicing generalists finding a welcoming home for their talents and commitments. They are proving their worth and they represent, if properly nurtured, a promising additional strength for the shifting spectrum of Medicine.

In closing, as I reflect upon these remarks, I believe they may serve as the real essence of this attempted tribute to Dr. Mack Lipkin.

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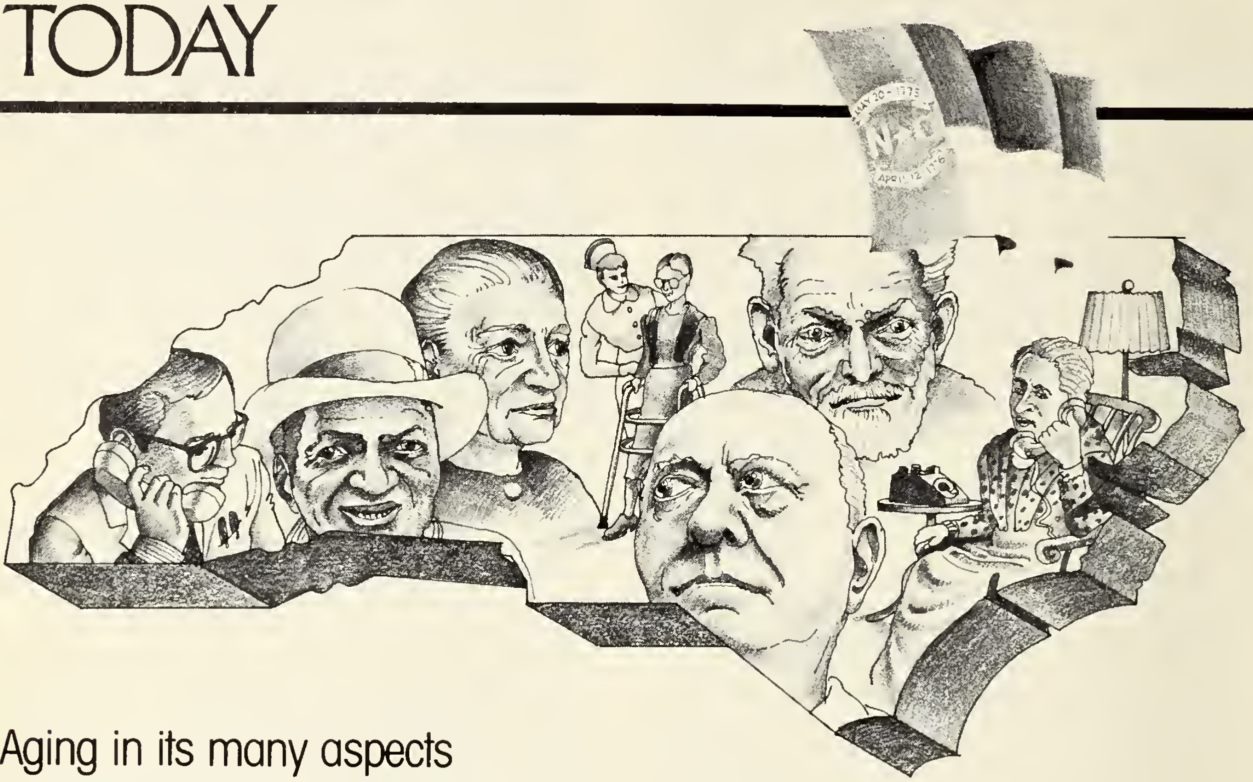

Aging in its many aspects

It is estimated that 25 million people (11% of the population) are over age 65, and represent the fastest-growing segment of the population by far. It is further estimated that this group currently spends approximately 75 billion dollars annually for personal health care, and accounts for some 55% of all federal health dollars.[1] For these reasons alone, studies concerned with various aspects of aging are of vital importance to the entire nation. Much major research in this complex area is being conducted in North Carolina, at its several medical centers and universities, often under grants from the National Institute on Aging.

Studies cover a wide range

Recent studies have reported on the physiological dynamics of aging as related to circulatory diseases and circulatory risk factors at advanced ages (over 85) as compared to findings in a study population with a mean age of over 70 years.[2] Another study, stemming from the comprehensive Duke First Longitudinal Study, evaluated Wechsler Memory Scale scores as related to distance from death and the potential use of the WMS as a predictor of survival in both normal and demented elderly populations,[3] while yet another compared young and old adults in the spontaneous use of context to learn and recall information.[4]

Dealing with America's fourth leading killer disease

Researchers at Duke University Center for the Study of Aging are focusing on the study of Alzheimer's disease, a type of primary neuronal degeneration that is the most common form of dementia. Estimates vary but indicate that as many as 4 million older Americans[1] are afflicted with this illness, which has been labeled "the disease of the century."[5] Concurrent with its medical research on Alzheimer's disease, the Duke University Center is providing innovative support mechanisms for afflicted families and other caretakers. A hotline provides callers with telephone consultations, introductions to others close by in similar circumstances, and practical medical, legal and psychological information. The Center has also aided in the establishment of 19 local support groups statewide, and regularly makes available information on Alzheimer's disease to health providers, nursing homes and hospitals, and others responsible for programs and services directed toward the victims of this killer disease.[6]

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*Feighner JP, *et al*: *Psychopharmacology* 61:217-225, Mar 22, 1979

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

> ***Usage in Pregnancy:*** **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

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Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

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SCIENTIFIC ARTICLE

Blood Replacement for Repeat Cesarean Section: "Type and Screen" Preferable to Cross Matching

David H. Chestnut, M.D.

Introduction

THE safety and efficacy of the type and screen in obstetric practice have been previously reported.[1-3] Time-honored practice patterns are slow to change, however; it is the author's observation that physicians commonly continue to request cross-matching of two units of blood for patients scheduled for repeat cesarean section. It is the purpose of this communication to report recent experience with blood replacement for patients undergoing repeat cesarean section in a university hospital.

Materials and Methods

The hospital records of all patients undergoing repeat cesarean section at Duke University Medical Center between November 1, 1981, and April 30, 1984, were retrospectively reviewed. Patients transfused preoperatively were excluded from the study.

Each patient chart was manually reviewed for collection of maternal parameters. Socioeconomic status was defined according to whether the patient was a private or a staff (resident physician) patient.

Results

Between November 1, 1981, and April 30, 1984, 218 patients underwent a repeat cesarean section at Duke University Medical Center. Five anemic patients were excluded from the study because they were transfused preoperatively. Table 1 includes maternal characteristics of the remaining 213 patients.

Eight of 213 patients underwent repeat cesarean after an unsuccessful trial of labor; an additional 61 patients were in early labor and/or had spontaneous rupture of membranes prior to repeat cesarean. The remaining 144 patients underwent elective repeat cesarean. Table 2 includes details of operative management.

Four patients (1.9%) were transfused intraoperatively. One patient with a placenta previa underwent emergency hysterectomy for intractable bleeding secondary to placenta accreta; this patient was transfused four units of blood intraoperatively and an additional three units postoperatively. The remaining three patients were transfused two units of blood intraoperatively; hemodynamic instability was not an indication for transfusion in these three patients.

Two patients were each transfused two units of blood within the first 24 postoperative hours. Thus six of 213 patients (2.8%) were transfused perioperatively.

An additional 11 patients were transfused after the first 24 postoperative hours but prior to discharge. These 11 patients received a total of 27 units of blood.

Ten of 213 patients had a preoperative hematocrit less than 30. Five of these ten patients were transfused either intraoperatively or postoperatively.

Mean hematocrit prior to discharge was 32.1. Mean postoperative hospital stay was 5.3 days.

Discussion

Reisner recently reported experience with blood replace-

Table 1
Maternal Characteristics

Number of patients	213	
Mean age	25.3	
Race: White	58	(27.2%)
Black	150	(70.4%)
Other	5	(2.3%)
Socioeconomic status: Private	50	(23.5%)
Staff	163	(76.5%)
Mean weight in pounds	168.2	
Mean weeks gestation	38.3	
Mean preoperative hematocrit	35.6	

Table 2
Operative Management

Anesthesia: General	108	(50.7%)
Epidural	103	(48.4%)
Spinal	2	(0.9%)
Uterine incision: Low transverse	209	(98.1%)
Vertical	4	(1.9%)
Tubal ligation	101	(47.4%)
Mean operative time in hours*	0.96	

* Excluding one patient undergoing cesarean hysterectomy; operative time for this patient was 2.7 hours.

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ment during repeat cesarean; one of 148 patients (0.7%) was transfused intraoperatively.[4] He did not report the socioeconomic status of the patient population or the incidence of postoperative transfusion. The data presented herein confirm a low incidence of perioperative transfusion in patients of primarily lower socioeconomic status undergoing a repeat cesarean section in a teaching hospital.

Had two units of blood been crossmatched for all 213 patients in this study, the perioperative crossmatch:transfusion ratio would have been 29.7, considerably higher than the recommended ratio of 2.1 to 2.7.[5] Routine preoperative crossmatching of two units of blood necessitates setting aside blood for a large number of patients who will not require transfusion. Such practice not only is time consuming for blood bank personnel, but also depletes the supply of reserved units for patients with more critical needs for transfusion. Crossmatched blood may exceed its expiration date without being utilized, and larger inventories are required.

The type and screen has been previously reported as a safe and efficacious alternative in obstetric practice.[1-3] Blood bank personnel initially determine the patient's ABO group and Rh factor. Patient serum is subsequently mixed with reagent red blood cells from two donors in order to screen for the presence of red blood cell antibodies. Unexpected antibodies are noted in 0.7 to 3.5% of patients;[1, 3, 6] compatible blood is then crossmatched preoperatively for these patients with a positive antibody screen.

If the antibody screen is negative, the blood bank technologist verifies that a reasonable quantity of ABO group- and Rh type-specific blood is available for transfusion. Should blood be urgently needed intraoperatively for the patient with a negative antibody screen, a 15 second saline spin using the patient's serum and donor red cells is performed to avoid transfusing incompatible blood secondary to clerical error. If the need for transfusion is less urgent, a crossmatch, utilizing both incubation of low ionic strength solution and an antiglobulin test, can be completed within 20 minutes. In one study of 23,857 patients, only 0.06% of patients had antibodies identified at the time of the crossmatch that had not been noted with the initial antibody screen, and most of these antibodies were thought to be insignificant during transfusion.[6] Thus the type and screen has been reported to be 99.99% effective in preventing the transfusion of incompatible blood.[7]

It is not surprising that utilization of the type and screen results in significant financial savings for the patient. At this medical center, the patient charge for a type and crossmatching of two units of blood is greater than three times the patient charge for a type and screen.

The committee on standards of the American Association of Blood Banks has stated that "guidelines for preoperative blood orders . . . should be based on local surgical transfusion utilization patterns, and must allow for modification for selected patients."[8] The presence of preoperative anemia, placenta previa, or coagulopathy may therefore prompt the physician to request a full crossmatch prior to performing repeat cesarean.[4, 9] The data presented herein, however, suggest that the type and screen deserves greater utilization by North Carolina physicians prior to performance of repeat cesarean section.

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See section under **Special Notes on Administration and HOW SUPPLIED.**
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DESCRIPTION
Norlestrin Products are progestogen-estrogen combinations

INDICATIONS AND USAGE
Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles there was a pregnancy rate of 0 05 per 100 woman-years, in clinical trials with Norlestrin 2 5/50 involving 96 388 cycles there was a pregnancy rate of 0 22 per 100 woman years

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance

CONTRAINDICATIONS
1 Thrombophlebitis or thromboembolic disorders
2 A past history of deep-vein thrombophlebitis or thromboembolic disorders
3 Cerebral vascular or coronary artery disease
4 Known or suspected carcinoma of the breast
5 Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding
7 Known or suspected pregnancy (See WARNING No 5)
8 Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

WARNINGS
Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke myocardial infarction hepatic adenoma, gallbladder disease and hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1 *Thromboembolic Disorders and Other Vascular Problems* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2 0 times greater in users than nonusers, and the risk of thrombotic stroke was 4 0 to 9 5 times greater

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not Oral contraceptives, however were found to be a clear additional risk factor

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke The amount of smoking is also an important factor

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women in those with a long duration of use and in cigarette smokers

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth with the exception of oral contraceptives in women over 40 who smoke

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders Should any occur or be suspected, the drug should be discontinued immediately

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization

2 *Ocular Lesions* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis have been associated with the use of oral contraceptives Discontinue the oral contraceptive if there is unexplained sudden or gradual partial, or complete loss of vision, onset of proptosis or diplopia, papilledema or retinal vascular lesions

3 *Carcinoma* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however an excess risk in users with documented benign breast disease was reported

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives Close clinical surveillance of users is nevertheless essential In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms, should be monitored with particular care

4 *Hepatic Tumors* Benign hepatic adenomas have been found to be associated with oral contraceptives Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives The relationship of these drugs to this type of malignancy is not known at this time

5 *Usage in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring* During early pregnancy female sex hormones may seriously damage the offspring

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods If the patient has not adhered to the schedule the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out If pregnancy is confirmed the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive

Administration of progestogen only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy

6 *Gallbladder Disease* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives

7 *Carbohydrate and Lipid Metabolic Effects* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives

An increase in triglycerides and total phospholipids has been observed

8 *Elevated Blood Pressure* An increase in blood pressure has been reported in patients receiving oral contraceptives The prevalence in users increases with longer exposure Age is also strongly correlated with development of hypertension Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure

9 *Headache* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent persistent or severe, requires discontinuation of oral contraceptives

10 *Bleeding Irregularities* Breakthrough bleeding, spotting and amenorrhea are frequent reasons for patients discontinuing oral contraceptives In breakthrough bleeding, nonfunctional causes should be borne in mind In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives

11 *Ectopic Pregnancy* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures

12 *Breast-Feeding* Oral contraceptives may interfere with lactation Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs

PRECAUTIONS
1 A complete medical and family history should be taken prior to the initiation of oral contraceptives The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination

2 Preexisting uterine leiomyomata may increase in size

3 Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree

4 Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring in patients with conditions which might be aggravated

5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice If jaundice develops, the medication should be discontinued

6 Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function

7 Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency

8 Serum folate levels may be depressed

9 The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted

10 Certain endocrine and liver function tests and blood components may be affected

(a) Increased sulfobromophthalein retention (b) Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone (d) Decreased pregnanediol excretion (e) Reduced response to metyrapone test

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates phenylbutazone, phenytoin sodium, tetracycline and ampicillin

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives thrombophlebitis, pulmonary embolism coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease benign hepatomas, congenital anomalies

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle Other reactions as a general rule, are seen much less frequently or only occasionally gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea amenorrhea during and after treatment temporary infertility after discontinuance of treatment, edema, chloasma or melasma, breast changes, change in weight change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature, intolerance to contact lenses

The following adverse reactions have been reported and the association has been neither confirmed nor refuted premenstrual-like syndrome, cataracts, changes in libido; chorea, changes in appetite cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption vaginitis, porphyria

Special Notes on Administration
Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day after discontinuing medication

After several months on treatment, bleeding may be reduced to a point of virtual absence, reduced flow may be a result of medication and not indicative of pregnancy

HOW SUPPLIED
Norlestrin [21] 1/50 is available in compacts each containing 21 tablets Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin [21] 2 5/50 is available in compacts each containing 21 tablets Each tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

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Norlestrin [28] 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

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EDITORIAL

Blood Replacement for Repeat Cesarean Section

Roy T. Parker, M.D.

SINCE World War II, the maternal mortality in North Carolina has been reduced from an average of 200 per 100,000 live births in the years 1945-1950 to 10 per 100,000 live births in the years 1976-1980. The maternal mortality rate is still three-fold higher in black women than in white, indicating a major influence of social, educational, and economic factors. Hemorrhage, hypertension (induced or aggravated by pregnancy) and infection were the primary major causes of maternal death. Hemorrhage is still a significant problem, but death from bleeding is of a different etiology than the classic abruptio placenta, placenta previa and postpartum atony of 40 years ago. The so-called "minor causes of bleeding" such as induced abortion, ectopic and intravascular coagulopathy are more prominent now that the death rate has been reduced primarily in the major causes. Nonetheless, there is no substitute for blood component therapy in acute blood loss and shock. Recognizing the vital influence of improved socioeconomic and educational factors and general medical care upon the decline of maternal mortality, the major advances in obstetric practice and obstetric facilities have been the *sine qua non* of saving the lives of mothers and babies. In 1945 there were fewer than 50 certified obstetricians and gynecologists in North Carolina and today there are more than 550. Equally striking is the fact that in North Carolina in 1945, greater than 50% of deliveries were in the home, whereas today over 98% are in hospitals. With regard to safety for mother and baby, *hospital delivery is a singular important factor*. The knowledge and skill to transfuse blood for obstetric hemorrhage in a hospital setting is a life-saving measure that cannot be challenged.

During this same interval since World War II, there has been an explosion of medical knowledge, research, and patient services that has made the U.S.A. the envy of the world, and North Carolina has shared fully in most of these medical advances. The results have been an inordinate increase in the number of physicians and hospitals, both federally sponsored, and without much regard for consequences. Medicine, through education, research and patient services, has created the nation's third largest industry, the cost of which is approaching $200 billion annually. The counterreaction now underway is to reduce physician output by 15%, to close smaller underutilized hospitals, to limit patient services, and to economize in patient care. This means that each and every hospital unit must seek ways to function effectively with less expenditure.

Elsewhere in this issue, Dr. Chestnut has presented a clinical study that demonstrates a means of reducing cost in the blood transfusion service for obstetric patients undergoing cesarean section, without compromising the safety of mother and baby. The average blood loss associated with a cesarean section is about one liter (twice that of a vaginal delivery), and not uncommonly it is greater. Therefore, the time honored practice to request cross-match of two units of blood for cesarean delivery is not without reason. Further, bleeding during delivery is most likely to be fatal to the mother when whole blood or blood components are not immediately available. The question is, can the "type and screen" provide the safety without the added cost of "type and crossmatch" and setting aside of two units of blood?

Of 213 patients who had repeat cesarean delivery in the Duke Medical Center between November 1, 1981 and April 30, 1984 and were eligible for review, four (1.9%) were transfused intraoperatively, and two additional patients were transfused within 24 hours, to equal 6 patients (2.8%) in the immediate perioperative phase of care. Thus, 207 patients and 414 bottles of blood would have been typed and cross-matched and set aside that were not needed in the "on demand" emergency situation.

The "type and screen" methodology is described and includes patient's ABO group, Rh factor, and red blood cell antibodies. Dr. Chestnut points out that unexpected antibodies are noted in 0.7 to 3.5% of patients and in such patients, compatible blood is cross matched preoperatively. For the remainder of patients, where an uncomplicated cesarean section is expected, the blood bank verifies that "a reasonable quantity of ABO group- and Rh type-specific blood is available for transfusion." Next, Chestnut reports that "should blood be urgently needed intraoperatively for the patient with a negative antibody screen, a 15-second saline spin, using the patient's serum and donor red cells, is performed to avoid transfusing incompatible blood secondary to clerical error. If the need for transfusion is less urgent, a crossmatch, utilizing both incubation of low ionic strength solution and an antiglobulin test, can be completed in 20 minutes." His study and literature reports (including large numbers of patients) show that the "type and screen" technique is 99.99% effective in preventing incompatible blood transfusions.

Dr. Chestnut's final admonition is that patients who have pre-existing conditions such as "anemia, placenta previa, or coagulopathy may therefore prompt the physician to

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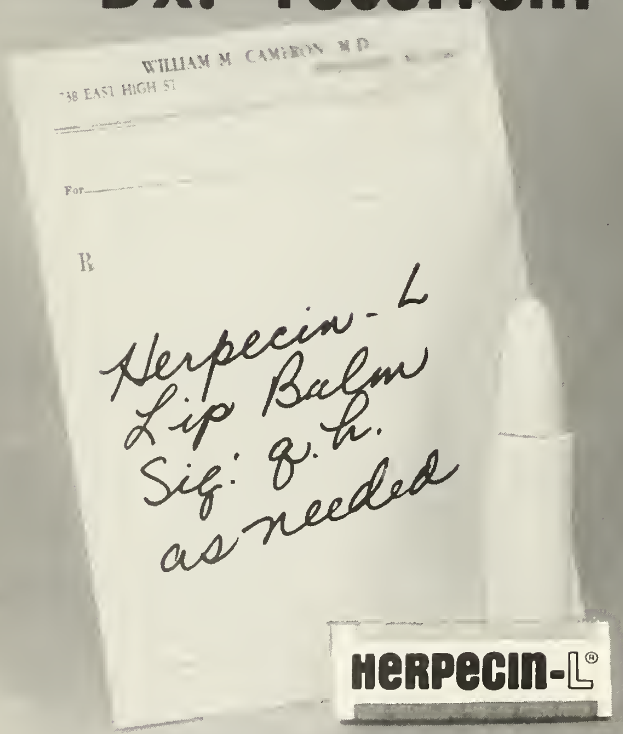
From the Department of Obstetrics and Gynecology, Duke University Medical Center, Durham 27710.

request a full crossmatch prior to performing repeat cesarean."

The "type and screen" methodology as described in this study and carried out in the Department of Obstetrics and Gynecology in the Duke Medical Center is safe for repeat cesareans and primary cesareans in healthy patients who do not have associated anemia or bleeding problems, provided that there is strict adherence to the outlined technique and the admonitions. My only concern is that other "shortcuts" will negate the experience gained during the past 40 years in preventing death from hemorrhage in obstetric patients.

Dx: recurrent herpes labialis



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EDITORIAL

Physicians Can and Should Offer Direction for the 1985 Legislature

Harold R. Silberman, M.D.

UNTIL recently, one issue that politically polarized many people has been how or whether religion should mix with government. Even on the Sunday before the General Assembly opened, some of our state legislators heard still another "sermon" on "Mixing Religion and Politics," this one by Dr. William H. Willimon speaking in Duke University's Chapel. Today, a much more urgent mixture should concern our profession . . . medicine and politics. In that interface, many questions are being raised. Are we being told how to practice? Is current and impending Federal legislation creating two classes of patients? Who is guiding government, at any level, toward implementing those regulations that help protect the interests of our patients and the health of all citizens?

Current newspapers focus on many significant issues confronting the 1985 General Assembly beginning with which political party has the real power and proceeding to Governor Jim Martin's 443.5 million dollar tax-cut proposal, while moving through a dozen other topics as diverse as highway priority, child pornography, phosphates in laundry detergent and gubernatorial succession.

Doctors have opinions on some or all of those matters to be sure. But major concerns of our North Carolina Medical Society will be addressed this session as well. In 1985, your Society plans to pursue and support legislation pertaining to: medical cost containment; preservation of local health departments; medical malpractice; allied health professionals; and traffic safety. It hopes to enhance motor vehicle safety in four specific areas: first, by a requirement that seat belts be used by everyone at all times; second, by urging re-enactment of G.S. 20-137.1, a bill that deals with compulsory application of child passenger restraint systems; third, by lobbying for a requirement to have both public land permits as well as age restrictions in order to engage in motor-cross racing; and fourth, by achieving immunity from any legal liabilities for those doctors who choose to report impaired drivers to the Division of Motor Vehicles.

Because physicians are trained to detect both physical and mental disabilities that could affect the ability of a person to operate a motor vehicle, they have sometimes been impotent witnesses to the beginnings of what will result in vehicular loss of life or serious injury. By current North Carolina statute, there is no obligation to report anything. There is always the moral duty, and recently, as in the Tarasoff case, *a responsibility* to *warn*, as neurologists will in the case of patients with seizure disorders. In that situation, most go beyond reminding their patients about the risks of operating an automobile and suggest reporting voluntarily their problem to the Department of Motor Vehicles. Almost always a note to that effect is written into the chart. But what about those patients who default after appropriate instruction? Then too, consider a much more frequent disease than epilepsy, namely chronic alcoholism. There the ethical question has two parts — should we report someone and to whom?

The North Carolina Medical Society wishes to establish a mechanism for reporting and to remove the stimulus not to report because of some fiduciary or confidential relationship existing between patients and their doctor. In May 1984, via direction from the Medical Society's Committee on Traffic Safety and through a recommendation from its Committee on Legislation, the Executive Council presented to the House of Delegates Report X: "RESOLVED, the North Carolina Medical Society recognizes the cost to society of allowing impaired drivers to operate motor vehicles and seeks legislation permitting physicians to report impaired drivers to the appropriate state officials and providing physicians making such a report with immunity from any and all liability." Your House of Delegates resoundly passed that resolution. Dr. H. David Bruton and his Committee on Legislation are now helping to draft a proposition which will be sponsored and brought to the General Assembly this spring. Of four different pieces of legislation in the area of motor vehicle safety, this is the only one that will be drafted and introduced by the Medical Society.

If you believe that immunizing your colleagues against civil liability will assist in keeping potentially unsafe drivers off the road, and that doing so will make a significant contribution toward reduction of the motor vehicle accident rate, then now is the time to make those beliefs known to a legislator. NCMS employs a staff in Raleigh willing and able to help you by providing names of legislators and advice about what to say or how to say it. Two very knowledgable individuals, Ann Sawyer, Governmental Affairs Director and Stan Williams, her Executive Assistant, can be reached at 1-800-722-1350.

These are risky times medically-legally speaking and many might doubt the capability of any law to provide protection against liability. Moreover, how one exercises medical discretion in reporting could potentially be cause for vulnerability to a lawsuit, especially if someone chooses to interpret a qualified privilege to report as a

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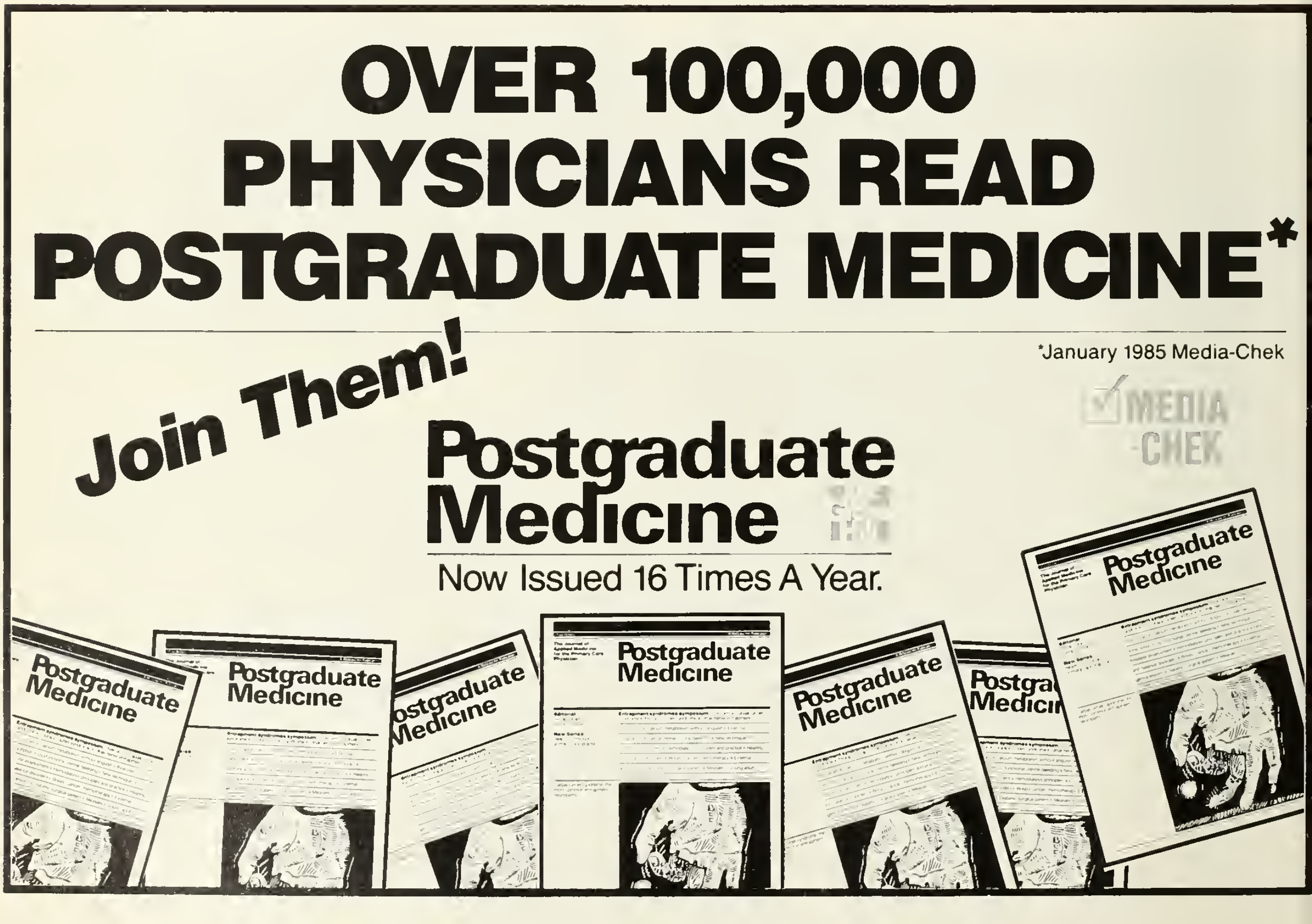
From the Department of Medicine, Duke University Medical Center, Durham 27710.

requirement to do so. Although current malpractice trends and a climate of culpability threaten to poison our atmosphere, they shouldn't prevent a meaningful dialogue between physicians and legislators. After all, for centuries we have been burdened by sometimes knowing more than we'd like to about our patients' bodies and minds. If some of that knowledge could potentially be used to promote better health for society as a whole, it should be.

Since most people listen and learn best at a time when they must consider a specific problem, I have mentioned to several State Representatives and Senators my interest in specific issues and offered them a paging beeper number so that they can reach me whenever *they* are ready to discuss a medical matter.



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Now contains naloxone, a potent narcotic antagonist

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No longer do doctors have to deny patients the benefit of an effective oral analgesic for fear of its misuse by injection.

Winthrop-Breon Laboratories has met a nagging problem by reformulating TALWIN® 50 (pentazocine HCl tablets) with the addition of naloxone, equivalent to 0.5 mg base. The reformulated product is called TALWIN® Nx.

The original formulation had been subject to a form of misuse among street abusers known as "T's and Blues." TALWIN 50 and PBZ,* an antihistamine, would be ground up together, put into solution, and injected intravenously. The combination produced a heroin-like high. Because naloxone is a narcotic antagonist when injected intravenously, it acts to nullify any high a "T's and Blues" addict might expect from the pentazocine in a combination of TALWIN Nx and PBZ. When taken as directed orally, the naloxone component of TALWIN Nx is inactive. Thus, TALWIN Nx continues to be a safe, effective, oral analgesic for the relief of moderate to severe pain, now providing added security against misuse.

*Registered trademark of Ciba-Geigy Corp for tripelennamine.

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T-540 NDC 0024-1951-04
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Each tablet contains pentazocine hydrochloride, USP, equivalent to 50 mg base and naloxone hydrochloride, USP, 0.5 mg.
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CIV Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0.5 mg base.

The reformulation of Talwin 50 to Talwin Nx involved the addition of 0.5 mg naloxone to help prevent misuse by injection.

Please see following page for Brief Summary.

Talwin® Nx Ⓒ IV

Each tablet contains pentazocine HCl, USP, equivalent to
50 mg base and naloxone HCl, USP, equivalent to 0 5 mg base.

Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone

> TALWIN® Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances (See **Drug Abuse and Dependence** section)

Warnings: *Drug Dependence* Can cause physical and psychological dependence (See **Drug Abuse and Dependence**) *Head Injury and Increased Intracranial Pressure.* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention, these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure Can obscure the clinical course of patients with head injuries, in such patients, use with extreme caution and only if deemed essential *Usage with Alcohol* Due to potential for increased CNS depressant effects, alcohol should be used with caution *Patients Receiving Narcotics.* Pentazocine is a mild narcotic antagonist Withdrawal symptoms have occurred in patients previously given narcotics, including methadone *Certain Respiratory Conditions* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis
Precautions: *CNS Effect* Use cautiously in patients prone to seizures, seizures have occurred though no cause and effect relationship has been established Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours Such patients should be very closely observed and vital signs checked, if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur *Impaired Renal or Hepatic Function* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects; it should be administered with caution in renal or hepatic impairment In long-term use, precautions should be taken to avoid increases in dose by the patient *Biliary Surgery* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures, the clinical significance of these findings is not yet known *Information for Patients* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants *Myocardial Infarction* Use with caution in patients with myocardial infarction who have nausea or vomiting *Drug Interactions Usage with Alcohol* See **Warnings**. *Carcinogenesis, Mutagenesis, Impairment of Fertility* No long-term studies in animals to test for carciriogenesis have been performed *Pregnancy Category C* Should be given to pregnant women only if clearly needed. *Labor and Delivery* Use with caution in women delivering premature infants Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown *Nursing Mothers* Caution should be exercised when administered to a nursing woman *Pediatric Use* Safety and effectiveness in children below the age of 12 years have not been established
Adverse Reactions: *Cardiovascular* Hypotension, tachycardia, syncope *Respiratory* Rarely, respiratory depression *CNS Acute CNS Manifestations* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted *Other CNS Effects* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor *Gastrointestinal* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress *Allergic* Edema of the face, dermatitis, including pruritus, flushed skin, including plethora *Ophthalmic* Visual blurring and focusing difficulty *Hematologic* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia *Other* Headache, chills, insomnia, weakness, urinary retention
Drug Abuse and Dependence: *Controlled Substance* TALWIN Nx is a Schedule IV controlled substance
Dependence and withdrawal symptoms have been reported with orally administered pentazocine Patients with a history of drug dependence should be under close supervision. Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient Tolerance to the analgesic effect is rarely reported, there is no long-term experience with oral use of TALWIN Nx
The amount of naloxone present (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine, however, this amount of naloxone given by injection has orofound antagonistic action to narcotic analgesics TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route
Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals
Overdosage: *Treatment* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated Assisted or controlled ventilation should also be considered For respiratory depression, parenteral naloxone is a specific and effective antagonist.

Please consult full product information before prescribing

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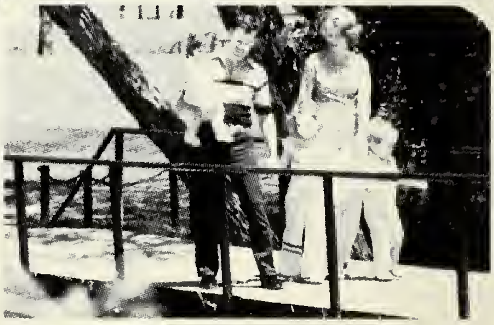

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Drugs Worked But How? Frederick Bernheim Unravels The Mystery

Frederick Bernheim, Ph.D.

WHEN I joined the Duke faculty in 1930, the nature of enzymes and their actions were not understood. In many ways they were similar to inorganic catalysts which were known to speed up and facilitate many chemical reactions. The fact that a large number of different enzymes had to be present to carry out the many chemical reactions necessary for life within a narrow range of temperatures was beginning to be appreciated. No one had a clear idea of the materials and their organization which could lead to such diversity in structure and function. The notion that enzymes might be proteins was unthinkable. It was known that enzyme activity did not require live intact cells. They had the property described as *élan vitale.*

In the early 1930s Sumner[1] crystallized a protein obtained from bean meal, carefully purified it, and showed that it acted as an enzyme to break down urea into ammonium carbonate. He called the protein urease. His troubles then began. No journal would publish his paper because it was unthinkable that a pure protein could be a catalytic enzyme. Eventually, his work was published and confirmed. Sumner started an area of intensive work on enzymes, their purification, structure and mechanism of action. Enzymes in body fluids were more easily concentrated and purified than those present in cells. When one homogenized cells, he obtained a soup containing many enzymes besides the one the investigator wished to study.

At this time we knew that drugs caused changes in body functions but we did not know how those changes were produced. Could it be that drugs attached themselves to enzymes or to the substrate of enzymes and altered thereby certain chemical effects? We knew that various drugs added to homogenates of cells or purified enzymes inhibited activity of the enzyme. We found out that the inhibition showed specificity in that a drug rarely affects more than one enzyme. I asked the question: can the inhibition of the enzyme explain the pharmacological effects seen when the drug is given to the animal?

When I began the attempt to answer this question, an affirmative answer was found in only two instances. Eserine inhibits isolated cholinesterase and prolongs acetylcholine effects in the animal as shown by Loewi,[2] and cyanide inhibits cytochrome oxidase, the enzyme essential for cell respiration,[3] rapidly kills the animal. I decided that it would be pertinent to test the effect of a number of other drugs on enzymes and then search the literature to determine how far enzyme action correlates with pharmacological action. Enzymes and substrates were where the action was. In 1940 I wrote a monograph on the results of my and others' work. It was entitled *The Interaction of Drugs and Cell Catalysts* and was published in 1942. The following is the table of contents of the monograph.

Frederick Bernheim, Ph.D., was born into a middle-class family in Long Branch, New Jersey. His father was a native of New York, New York and his mother of Wilmington, North Carolina. He was educated in the Ethical Culture School, Andover, Harvard, Cambridge, England. He wanted to become an M.D. but his mother became one "after more or less raising me and two younger brothers. For complicated psychological reasons, this made it impossible for me to study medicine so I settled for a career in biomedical research." Professor Bernheim donated the original 70 acres for the Eno River Park in Durham.

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From the Department of Pharmacology, Duke University Medical Center, Durham 27710.

b) Other Enzymes
    - Cyanide
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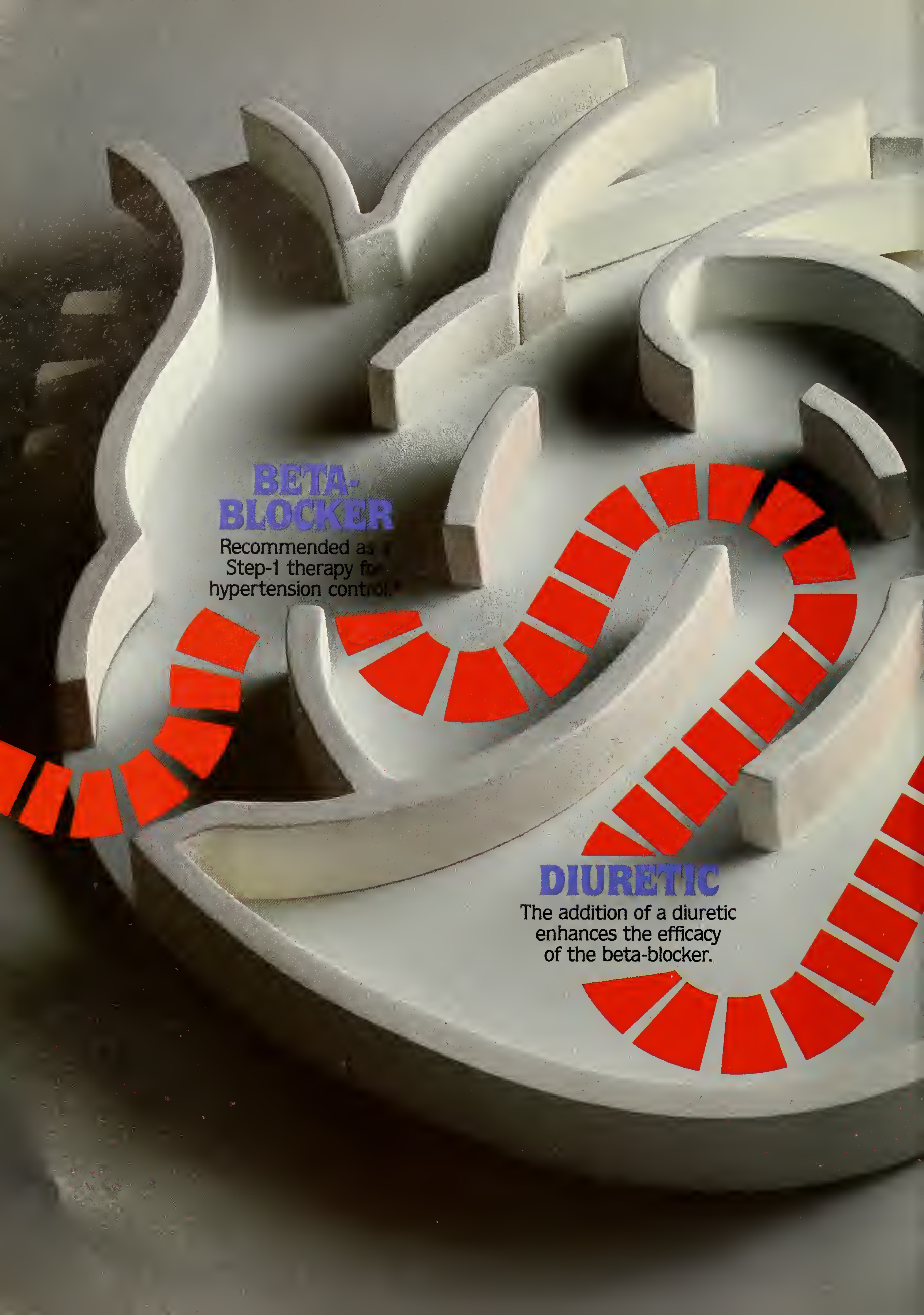
The appreciation of the great diversity of enzymes and the knowledge that the attachment of drugs to these structures would change their organization and activity has taken the mystery out of pharmacology and allowed understanding at the molecular level. I am pleased that my position in the Duke Medical School gave me a stable platform to explore basic pharmacology and to have a role in understanding how drugs have their effect.

References

1. Sumner JB. J Biol Chem 1926; 69:435.
2. Englehart E, Loewi O. Arch Exp Path Pharmacol 1930; 150:1.
3. Warburg O. Z Physiol Chem 1910; 70:413.

The Logical Path to Compliance



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Innovators in cardiovascular medicine

*Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. The 1984 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 144:1045-1057, 1984.

Please see brief summary of prescribing information on following page

CORZIDE®

(nadolol-bendroflumethiazide tablets)

CORZIDE® 40/5
CORZIDE® 80/5
Nadolol-Bendroflumethiazide Tablets

DESCRIPTION: CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration combines two antihypertensive agents: CORGARD® (nadolol), a nonselective beta-adrenergic blocking agent, and NATURETIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations: 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide.

CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). **Bendroflumethiazide** — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS: Nadolol — **Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — **Nadolol** — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and G.I. disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, *Bendroflumethiazide*, and PRECAUTIONS, *General, Bendroflumethiazide).*

Drug Interactions — **Nadolol** — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents: **Anesthetics, general** — exaggeration of anesthetic-induced hypotension (see WARNINGS, *Nadolol, Major Surgery).* **Antidiabetic drugs (oral agents and insulin)** — hypoglycemia or hyperglycemia, adjust antidiabetic drug dosage accordingly (see WARNINGS, *Nadolol, Diabetes and Hypoglycemia).* **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect, monitor closely for evidence of hypotension and/or excessive bradycardia.

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics: **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of antidiabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or peripheral adrenergic blocking drugs** — potentiated effect. **Preanesthetic and anesthetic agents** — effects may be potentiated, adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, *General, Bendroflumethiazide).*

Carcinogenesis, Mutagenesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed.

Pregnancy — **Teratogenic Effects** — **Nadolol** — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus; these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol-Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported, intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling, weight gain; slurred speech; cough; nasal stuffiness; sweating, tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol. The following adverse reactions may also occur: **Central Nervous System** — reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss; emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat, laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia, Peyronie's disease; erythematous rash; arterial insufficiency.

Bendroflumethiazide — **Gastrointestinal System** — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersensitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed. Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, employ the following measures, as appropriate. **Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation. **Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a beta$_2$-stimulating agent and/or a theophylline derivative. **Stupor or Coma** — Supportive therapy as warranted. **Gastrointestinal Effects** — Symptomatic treatment as needed. **BUN and/or Serum Electrolyte Abnormalities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

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Good Grief Makes Good Sense

J. Trig Brown, M.D.

It is as inevitable as death and taxes: we all have or will experience losses during our lives. Our normal and expected reaction to loss is called the grief reaction. This reaction is characterized by a series of feelings, both mental and physical, which, if allowed to be expressed, helps us adapt to the loss. Good grieving, that is, completely working through the stages of grief, is very important to long-term health. Although we usually only think of grief occurring after the death of a close acquaintance, the same feelings can and should follow any significant loss (financial, health, possessions, etc.). Moving through the stages of grief in a normal fashion will be demonstrated in the following narrative.

The Normal Grief Reaction

Mrs. B., already nervous because her husband was unusually late this evening, had her greatest fears confirmed when she saw the State Trooper at her front door. "There has been an accident, Mrs. B., and I'm terribly sorry to have to tell you that your husband has been killed," the Trooper began.

"Oh my God, no, it can't be true. . . . I just don't believe it," the distraught woman cried as the rest of the Trooper's message went unheard. Suddenly, calming herself, she motioned the Trooper in and asked him to repeat the story.

"There must be a mistake, how can you be sure it was my husband?" she replied. She listened and then rejected his story for a third time until a neighbor arrived. He, too, knew of the accident; in fact, he had positively identified the body. The tears on his face confirmed the Trooper's news and Mrs. B. sighed, shook her head, and then burst into uncontrollable sobbing.

The next few days passed in a blur for Mrs. B. She wonders how she had the strength to make the decisions regarding the funeral service, remembers hoping and praying that it had all been a mistake, and remembers the devastating feeling when, finally seeing her husband's body at the chapel, she could no longer deny his death.

This woman is experiencing that phase of the grief reaction known as the **Shock Phase.** This typically begins immediately after learning about the loss and lasts for a few days. The most striking feature of this period is to feel numb and for the loss to seem unreal. As demonstrated by the above narrative, Mrs. B. tended to not believe the news of her husband's death until she finally saw his body, thus undeniably confirming the reality of the loss.

This Shock Phase is protective. By holding on to partial hope that the loss is not real, we are able to function during the time immediately after the loss. If we did not have this protective numbing ability, the full sense of the loss would likely overwhelm most of us.

During this time sensations of throat tightness, abdominal emptiness, poor appetite, and crying spells are common. As the numbness and sense of unreality gradually fade, the knowledge that the loss is real is solidified and we enter the second phase of the grief reaction, the **Preoccupation Phase.**

Mrs. B. looks back on the months following her husband's death as the most difficult of her life. Thoughts of her husband were on her mind constantly. In the afternoons she would anticipate his return from work at the usual time and then, painfully remembering his death, tears would flow. Certain sights, sounds, and activities would bring a shower of painful memories of her husband. The memories felt when she glanced at their wedding picture were so sad and painful that she finally had to place it face down in a desk drawer.

She dearly loved her husband and yet some of the memories were not

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pleasant. They had had their normal share of conflicts and when she recalled those discussions she would feel an enormous amount of guilt. At times she even felt angry at him for leaving her and this served to make her feel even more guilty.

Often unable to sleep she would lay awake calling to mind times they had spent together. On a few occasions, she had vivid dreams of being with her husband and one time even had a strong sense that he was in the bed with her. In these dreams he appeared very comfortable and this left her with a peaceful feeling.

Mrs. B. found it difficult to resume participation in her usual activities and isolated herself socially. She did visit her doctor on two occasions because she had no appetite, had lost five pounds, and felt fatigued both day and night. After some blood tests the doctor reassured her that these symptoms were expected during this grieving period. Indeed, Mrs. B. found that these symptoms did lessen shortly after the doctor's visit.

Our narrative finds this recent widow in the midst of the second phase of the grief reaction, the **Preoccupation Phase.** This phase begins as the emotional "numbness" of the first phase lessens and the sense of the loss becomes more real. As in this example the grieving person is preoccupied with memories of the dead friend or relative. Every aspect of their lives together is relived through recalling past events.

In order to be able to form emotional attachments in the future, we must first give up the ties to the lost one. By moving through this second phase of grief the lost relationship is closely examined, the emotions stirred up by the loss are expressed, and gradually we are able to move forward again in life.

The feelings of sadness, anger, and even guilt are normal as past conflicts and problems are remembered. These feelings can be so strong and painful that the grieving individual might actually interrupt the grieving process at this time, resume normal activities too quickly, and thus be set up in the future for potential problems.

Some decrease in appetite and weight is normal during this phase. Sleep difficulty and vivid dreams of the deceased are not unusual. At times dreams can be so real that they take on a life-like character with visual images of the deceased. Weakness and fatigue are not uncommon during this second phase; however, these same symptoms can represent more serious medical problems and should be evaluated by a medical doctor if there is any question.

Gradually Mrs. B.'s life began to return to normal. As her sleeping approached normal, her weakness and fatigue waned. Dreams of her husband become rarer. Previous activities again became pleasing and she resumed many of her social activities.

This gradual improvement was interrupted by a return of the sleep difficulty, decreased appetite, and fatigue. Another visit to her doctor uncovered the fact that these symptoms were occurring at the first year anniversary of her husband's death. Again these symptoms went away on their own. She noticed similar but briefer difficulties at holiday times.

Although she still thought about her husband often, the memories gradually evoked less pain. She became able to think about past activities and places with pleasure and not with tears. Their wedding picture, stashed away because of the painful feelings seeing it produced, once again found its place on the desk.

The third and final phase of the grief reaction is the **Resolution Phase.** As the manifestations of the second phase gradually diminish we are less preoccupied with the thoughts of the deceased and less socially disabled. As Mrs. B.'s course demonstrates, the grieving individual may notice a return of the sadness, sleep difficulty, and other manifestations of the second phase of grief at certain significant times. These are known as "anniversary reactions" and examples include the anniversary of the death, the deceased's birthday and holidays. These setbacks are usually temporary and disappear on their own.

The length of the normal grief reaction varies; however, most note some progress toward resolution by at least six to eight months. By 12 months the grief reaction is usually completed and once again the person is able to think about the past with pleasure, activities that had been curtailed are again interesting, and new relationships can be formed.

Guidelines for Good Grieving

Time normally heals the wounds of losses. There are some people, however, who do not proceed through the phases of grief normally. These people may develop depression, social isolation, difficulties with other relationships, and other medical problems in the future because of this incomplete grieving. During the grieving period it is difficult for the person closest to the loss to recognize an abnormal grief response; thus these guidelines are being presented for those close to the person who has experienced the loss. With these points in mind we may better be able to help our friends, family members, and perhaps ourselves to cope with losses.

1. Prepare

Although some losses are sudden and unexpected, the majority of losses we experience can to some degree be anticipated. Preparing for future losses is called "anticipatory grief" and helps adjust to the loss once it occurs. During a lengthy terminal illness we should be talking with our loved ones, expressing both the joys of having them and the anticipated sorrows of being apart. We should ensure that things we want to say to this person are said; it is much better to know that you have expressed yourself than to have to hope that they somehow knew what you wanted to say. Get financial affairs in order; knowledge of financial stability for dependents is very comforting to most terminally ill people. By all means do not shun the topic of the person's illness. If a terminally ill person senses that you cannot deal with the issue, he or she may have more difficulty in coping also.

2. Grieve

Not grieving is bad grieving. We have all seen the person who showed little or no emotional reaction to a loss. "She surprised us; she was so strong and didn't break down and fall apart," may be a harbinger of problems and not necessarily a statement of strength. It should be stressed again that the grief reaction is normal and necessary and absent grief may mean that the person is too overwhelmed by the painful emotions produced by thinking about the loss to allow any expression of sadness. These people, by denying the truth of the loss, are at risk to develop problems in the future. People who express no grief should be encouraged to discuss what the loss means to them, in this supportive way hearing that it is okay to grieve.

3. Talk

Talking is the best way to ensure that the grief reaction proceeds normally. People with recent losses should be encouraged to talk about the loss, their life before and after the loss, and to express the emotions that surge forth when discussing these issues. Sharing feelings and experiences and crying together is beneficial. Anger and guilty feelings may make it too painful for these issues to be discussed. In such cases talking to professional counselors is helpful.

4. Participate

In our society there are a number of rituals which assist our grieving. Full participation in these activities should be encouraged. Viewing the body, the memorial service, and the graveside ceremony help us grasp the reality of the loss and move the grief reaction forward. After a loss, family and friends gather, thus adding social support to those who are in need. Business matters and financial affairs often require attention and the recently bereaved should participate in these. Articles of clothing and possessions should be sorted through, saving some and giving others away. This act helps start the process of sorting through memories, a crucial step in getting over the loss. At every stage in the grieving process we should urge the active participation of those involved.

Prepare, grieve, talk, and participate are four actions that will help the grief reaction flow in a normal manner. The overall goal is to allow us to examine our emotional attachments and to express the feelings that the loss produces. Through this process, we will then be able to adjust to the changes created by the loss. We should prevent abnormal grief reactions because they can have detrimental effects upon health. If you have questions about your own reaction to loss or about a friend's or family member's reaction, ask your doctor. This health issue deserves attention.

When To See Your Doctor About Vertigo and Dizziness

Marvin P. Rozear, M.D.

Vertigo means an abnormal feeling that you are standing still and other things are moving or vice versa (when your intellect tells you that neither you nor your surroundings are moving). This is the feeling you get after you spin around in circles a few times, or get off a merry-go-round. In strictest terms, it is an illusion or hallucination (of movement).

Dizziness is a more nonspecific term which includes vertigo, but also a lot of other things people call lightheadedness, woaziness, faintness, but which do not necessarily include the illusion of motion. Some authorities say vertigo is more often due to actual disturbance of the balance organs of the inner ear or their brain connections, while dizziness is more nonspecific and more often due to other factors which affect the whole brain diffusely, such as low blood sugar, low blood pressure, fainting, nervousness, etc.

In my experience, the distinction does not carry much weight: some people who have clear-cut disturbances of their inner ears report that they were just woozy but not experiencing the sensation of motion. Furthermore, the only time I ever fainted, due to a sudden drop in blood pressure, I clearly experienced the room as spinning around. I remember it vividly. The room was going right to left.

The point is that the exact quality of the symptom may not be so terribly important. Well then, what is? I feel three things are important: (1) the progression of the dizziness, (2) what brings on the dizziness and (3) what it is associated with.

Using these features, I think we can construct a list of things which indicate that the dizziness requires medical attention, and these include:

1) constant or progressive dizziness, especially associated with hearing loss;
2) dizziness associated with other symptoms such as visual disturbance (especially double vision), numbness, or weakness in any body part;
3) dizziness associated with recurrent vomiting;
4) dizziness which lasts for more than a few seconds on standing up.

There are some types of dizziness that are much more benign and don't necessarily warrant medical attention:

1) intermittent dizziness with long periods of well-being between spells;
2) dizziness which comes on only in certain positions (especially lying down certain ways) and goes away in 10-20 seconds even though you maintain this position;
3) the dizziness associated with certain activities such as riding in the back seat of a car or looking down from high places.

If you feel that your dizziness falls into the "bad" category above, and that it warrants medical attention, the next question that comes up is "how soon should I seek medical attention?" We can be guided by the degree of sickness experienced here: If this has been slowly progressing over several months and has not yet caused any great disability, you could make an appointment with a physician and be seen in the next few weeks. On the other hand, if you are suddenly seized in the morning by intense dizziness associated with severe nausea, vomiting, double vision, and a headache, you should go to the nearest emergency facility as soon as possible.

One more comment. Dizziness can be a very difficult symptom for patients to deal with and communicate about and therefore many doctors are uncomfortable in trying to help dizzy patients. If time permits and your dizziness does not seem to be an urgent or emergent problem, you might do well to ask around and find out if there is a doctor in your community or nearby who has shown an interest in dizziness or who has been helpful to a friend or neighbor in the past. Frequently, neurologists or otolaryngologists are more interested in dizziness than are other doctors, although this is certainly not an absolute rule.

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Rubella Prevention

Live Rubella Virus Vaccine

The live virus vaccine* currently distributed in the United States is prepared in human diploid cell culture. In January 1979, this vaccine (RA 27/3) replaced the HPV-77:DE-5 vaccine grown in duck embryo cell culture. Although both subcutaneous and intranasal administration of the vaccine have been studied, it is licensed only for subcutaneous administration. The vaccine is produced in monovalent form (rubella only) and in combinations: measles-rubella (MR), rubella-mumps, and measles-mumps-rubella (MMR) vaccines.

In clinical trials, 95% or more of susceptible persons who received a single dose of rubella vaccine when they were 12 months of age or older developed antibody. Clinical efficacy and challenge studies have shown that more than 90% of vaccinees can be expected to have protection against both clinical rubella and asymptomatic viremia for a period of at least 15 years. Based on available followup studies, vaccine-induced protection is expected to be lifelong. Therefore, a history of vaccination is presumptive evidence of immunity.

Although vaccine-induced titers are generally lower than those stimulated by rubella infection, vaccine-induced immunity usually protects against both clinical illness and viremia after natural exposure. There have been, however, a small number of reports indicating that viremic reinfection following exposure may occur in vaccinated individuals with low levels of detectable antibody. The frequency and consequences of this phenomenon are currently unknown, but its occurrence is believed rare. Such reports are to be expected, since there are also rare reports of clinical reinfection and fetal infection following natural immunity.

Some vaccinees intermittently shed small amounts of virus from the pharynx 7-28 days after vaccination. However, studies of more than 1,200 susceptible household contacts and experience gained over 15 years of vaccine use have yielded good evidence that vaccine virus is not transmitted. These data indicate that vaccinating susceptible children, whose mothers or other household contacts are pregnant, does not present a risk. Rather, vaccination of such children provides protection for these pregnant women.

Vaccine Shipment and Storage

Administering improperly stored vaccine may result in lack of protection against rubella. During storage, before reconstitution, rubella vaccine must be kept at 2°C-8°C (35.6 F-46.4 F) or colder. It must also be protected from light, which may inactivate the virus. Reconstituted vaccine should be discarded if not used within 8 hours. Vaccine must be shipped at 10°C (50 F) or colder and may be shipped on dry ice.

Vaccine Use

General Recommendations

Persons 12 months of age or older should be vaccinated, unless they are immune. Persons can be considered immune to rubella only if they have documentation of

1. laboratory evidence of rubella immunity or

2. adequate immunization with rubella vaccine on or after the first birthday. The clinical diagnosis of rubella is unreliable and should not be considered in assessing immune status.

All other children, adolescents, and adults — particularly women — are considered susceptible and should be vaccinated if there are no contraindications (see below). This includes persons who may be immune to rubella but who lack adequate documentation of immunity. Vaccinating children protects them against rubella and prevents their spreading the virus. Vaccinating susceptible postpubertal females confers individual protection against rubella-induced fetal injury. Vaccinating adolescent or adult females and males in high-risk population groups, such as those in colleges, places of employment, or military bases, protects them against rubella and reduces the chance of epidemics. This is exemplified by the experience with vaccinating all military recruits, which has virtually eliminated rubella from military bases. Similar results could be achieved by ensuring proof of immunity of all employees, all college students and staff, and all hospital personnel, including physicians, nurses, health-profession students, technicians, dietary workers, etc.

As discussed above, it is generally believed that any detectable antibody titer specific for rubella (whether resulting from vaccination or from naturally acquired rubella), even if very low, should be considered evidence of protection against subsequent viremic infection — including the reported "reinfection" of persons with low levels of antibody demonstrated by boosts in antibody titer. This suggests that immune females reinfected during pregnancy would be unlikely to infect their fetuses. Moreover, because there is very little pharyngeal excretion, there appears to be no risk to susceptible contacts in such reinfection settings. In view of the data on reinfection accumulated during the past decade the Immunization Practices Advisory Committee (ACIP) sees no reason to revaccinate persons with low levels of rubella antibody. Rather, more attention should be directed toward vaccinating the truly susceptible population.

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* Official name: Rubella Virus Vaccine, Live. From Morbidity and Mortality Weekly Report, June 8, 1984.

Dosage

A single dose of 0.5 cc of reconstituted vaccine (as a monovalent or preferably a combination product such as MR or MMR) should be administered subcutaneously.

Age at Vaccination

Live rubella virus is recommended for all children 12 months of age or older. It should not be given to younger infants, because persisting maternal antibodies may interfere with seroconversion. When the rubella vaccine is part of a combination that includes the measles antigen, the combination vaccine should be given to children at 15 months of age or older to maximize measles seroconversion. Older children who have not received rubella vaccine should be vaccinated promptly. Because a history of rubella illness is not a reliable indicator of immunity, all children should be vaccinated unless there are contraindications (see below).

Vaccination of Women of Childbearing Age

The ACIP has weighed several factors in developing recommendations for vaccinating women of childbearing age against rubella. Although there may be theoretical risks in giving rubella vaccine during pregnancy, available data on previously and currently available rubella vaccines indicate that the risk, if any, of teratogenicity from live rubella vaccines is quite small. As of December 31, 1983, CDC has followed to term 214 known rubella-susceptible pregnant females who had been vaccinated with live rubella vaccine within 3 months before or 3 months after conception. Ninety-four received HPV-77 or Cendehill vaccines, one received vaccine of unknown strain, and 119 received RA 27/3 vaccine. None of the 216 babies (two of the mothers receiving RA 27/3 vaccine delivered twins) has malformations compatible with congenital rubella infection. This finding includes the four infants born to these susceptible women who had serologic evidence of subclinical infection. (Three of the infants were exposed to HPV-77 or Cendehill vaccine; one was exposed to RA 27/3 vaccine.)

Based on the experience to date, the maximum estimated theoretical risk of serious malformation attributable to RA 27/3 rubella vaccine, derived from the binomial distribution, is 3%. (If the 95 susceptible infants exposed to other rubella vaccines are included, the maximum theoretical risk is 1.7%). However, the observed risk with both the HPV-77 or Cendehill and RA 27/3 strains of vaccine is zero. In either case, this risk is far less than the 20% or greater risk of congenital rubella syndrome associated with maternal infection during the first trimester of pregnancy.

Although experience with the RA 27/3 vaccine is more limited than that with the other rubella vaccines, rubella vaccine virus has been isolated from abortion material from one (3%) of 32 susceptible females who had been given RA 27/3 vaccine while pregnant, whereas virus was isolated from abortion material from 17 (20%) of 85 susceptible females who had been given HPV-77 or Cendehill vaccines while pregnant. This provides additional evidence that the RA 27/3 vaccine does not pose any greater risk of teratogenicity than did the HPV-77 or Cendehill vaccines.

Therefore, the ACIP believes that the risk of vaccine-associated defects is so small as to be negligible and should not ordinarily be a reason to consider interruption of pregnancy. However, a final decision about interruption of pregnancy must rest with the individual patient and her physician.

The continuing occurrence of rubella among women of childbearing age and the lack of evidence for teratogenicity from the vaccine indicate strongly that increased emphasis should continue to be placed on vaccinating susceptible adolescent and adult females of childbearing age. However, because of the theoretical risk to the fetus, females of childbearing age should receive vaccine only if they say they are not pregnant and are counseled not to become pregnant for 3 months after vaccination. In view of the importance of protecting this age group against rubella, reasonable practices in a rubella immunization program include: (1) asking females if they are pregnant, (2) excluding those who say they are, and (3) explaining the theoretical risks to the others.

Use of Vaccine Following Exposure

There is no conclusive evidence that giving live rubella virus vaccine after exposure will prevent illness. Additionally, there is no evidence that vaccinating an individual incubating rubella is harmful. Consequently, since a single exposure may not cause infection and postexposure vaccination will protect an individual exposed in the future, vaccination is recommended, unless otherwise contraindicated.

Use of Human Immune Globulin Following Exposure

Immunoglobulin (IG) given after exposure to rubella will not prevent infection or viremia, but it may modify or suppress symptoms and create an unwarranted sense of security. The routine use of IG for postexposure prophylaxis of rubella in early pregnancy is not recommended. Infants with congenital rubella have been born to women given IG shortly after exposure. IG might be useful only when a pregnant woman who has been exposed to rubella would not consider termination of pregnancy under any circumstances.

Recent Administration of IG

Vaccine should be administered about 2 weeks before or deferred for about 3 months after receipt of IG, because passively acquired antibodies might interfere with the response to the vaccine. On the other hand, previous administration of anti-RJa (D) immune globulin (human) or blood products does not generally interfere with an immune response and is not a contraindication to postpartum vaccination. However, in this situation, 6- to 8-week postvaccination serologic testing should be done on those who have received the globulin or blood products to assure that seroconversion has occurred. Obtaining laboratory evidence of seroconversion in other vaccinees is not necessary.

Side Effects and Adverse Reactions

Children sometimes have vaccine side effects, such as low-grade fever, rash and lymphadenopathy. Up to 40% of vaccinees in large-scale field trials have had joint pain, usually of the small peripheral joints, but frank arthritis has generally been reported for fewer than 2%. Arthralgia and transient arthritis occur more frequently and tend to be more severe in susceptible women than in children. While up to 3% of susceptible children have been reported to have arthralgia, arthritis has rarely been reported in these vaccinees. By contrast, up to 10%-15% of susceptible female vaccinees have been reported to have arthritis-like signs and symptoms. Transient peripheral neuritic complaints, such as paresthesias and pain in the arms and legs, have also very rarely occurred.

When joint symptoms or nonjoint-associated pain and paresthesias do occur, they generally begin 3-25 days (mean 8-14 days) after immunization, persist for 1-11 days (mean 2-4 days) and rarely recur. Adults with joint problems usually have not had to disrupt work activities. The occasional reports of persistent or recurrent joint signs and symptoms probably represent a rare phenomenon. No joint destruction has been reported. While the presence of immune complexes following vaccination has been reported to be associated with arthralgia and arthritis, the available data are still inconclusive. Comparable studies on naturally infected persons have not been conducted. Likewise, there is no clear association between joint symptoms and persistence of rubella virus in lymphocytes.

The vast majority of published data indicate that only susceptible vaccinees have side effects of vaccination. There is no conclusive evidence of an increased risk of these reactions for persons who are already immune when vaccinated.

Although vaccine is safe and effective for all persons 12 months of age or older, its safety for the developing fetus is not fully known. Therefore, though the risk, if any, appears to be minimal, rubella vaccine should not be given to women known to be pregnant because of the theoretical risk of fetal abnormality caused by vaccine virus (see above).

Precautions and Contraindications

Pregnancy

Pregnant women should not be given rubella vaccine. If a pregnant woman is vaccinated or if she becomes pregnant within 3 months of vaccination, she should be counseled on the theoretical risks to the fetus. As noted above, rubella vaccination during pregnancy should not ordinarily be a reason to consider interruption of pregnancy. Instances of vaccination during pregnancy should be reported through state health departments to the Division of Immunization Center for Prevention Services, CDC.

Because of the increasing number of cases reported to CDC, the experience with known susceptibles is becoming well defined. Therefore, CDC now encourages reporting only cases involving women known to be susceptible at the time of vaccination.

Febrile Illness

Vaccination of persons with severe febrile illness should be postponed until recovery. However, susceptible children with mild illnesses, such as upper respiratory infection, should be vaccinated. Considering the importance of protecting against rubella, medical personnel should use every opportunity to vaccinate susceptible individuals.

Allergies

Hypersensitivity reactions very rarely follow the administration of live rubella vaccine. Most of these reactions are considered minor and consist of wheal and flare or urticaria at the injection site.

Live rubella vaccine is produced in human diploid cell culture. Consequently, a history of anaphylactic reactions to egg ingestion needs to be taken into consideration only if measles or mumps antigens are to be included with rubella vaccine.

Since rubella vaccine contains trace amounts of neomycin (25 µg), persons who have experienced anaphylactic reactions to topically or systematically administered neomycin should not receive rubella vaccine. Most often, neomycin allergy is manifested as a contact dermatitis, which is a delayed-type (cell-mediated) immune response, rather than anaphylaxis. In such individuals, the adverse reaction, if any, to 25 µg of neomycin in the vaccine would be an erythematous, pruritic nodule or papule at 48-96 hours. A history of contact dermatitis to neomycin is not a contraindication to receiving rubella vaccine. Live rubella vaccine does not contain penicillin.

Altered Immunity

Replication of live rubella vaccine virus may be potentiated in patients with immune deficiency diseases and by the suppressed immune responses that occur with leukemia, lymphoma, generalized malignancy, and therapy with corticosteroids, alkylating drugs, antimetabolites, and radiation. Patients with such conditions should not be given live rubella virus vaccine. Since vaccinated persons do not transmit vaccine virus, the risk to these patients of being exposed to rubella may be reduced by vaccinating their close susceptible contacts. Management of such patients, should they be exposed to rubella, can be facilitated by prior knowledge of their immune status.

Patients with leukemia in remission whose chemotherapy has been terminated for at least 3 months may receive live virus vaccines for infections to which they are still susceptible (i.e., have neither had the disease nor the vaccine before developing leukemia). The exact interval after discontinuing immunosuppression that coincides with the ability to respond to individual vaccines is not known. Experts vary in their judgments from 3 months to 1 year.

Short-term (less than 2 weeks) corticosteroid therapy, topical steroid therapy (e.g., nasal, skin), and intra-articular, bursal, or tendon injection with corticosteroids should not be immunosuppressive and do not necessarily contraindicate live virus vaccine administration. However, live vaccines should be avoided if systemic immunosuppressive levels are reached by topical application.

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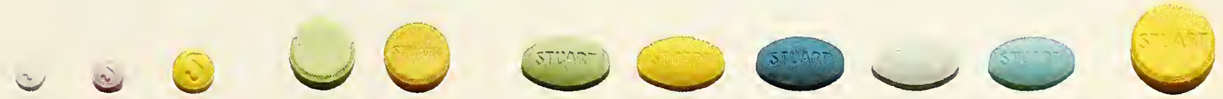

2.5 mg 5 mg 10 mg
Sublingual Tablets

5 mg 10 mg
Chewable Tablets

5 mg 10 mg 20 mg 30 mg 40 mg
Oral "Swallow" Tablets

40 mg
Sustained Action
"Swallow" Tablets

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See following page for brief summary of prescribing information.

SORBITRATE®

(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related In clinical trials at various doses, the following have been observed

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended The extent to which development of tolerance should modify the dosage program has not been defined *The oral controlled-release forms of isosorbide dinitrate should not be chewed*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg)

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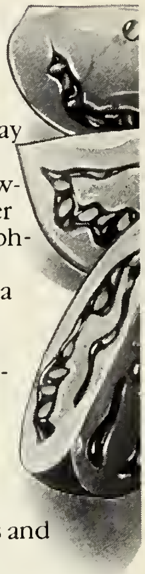


There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.

Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash, and tomatoes, citrus fruits and brussels sprouts.

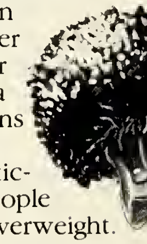
Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

Be moderate in consumption of alcohol also.

A good rule of thumb is cut down on fat and don't be fat. Weight reduction may lower cancer risk. Our 12-year study of nearly a million Americans uncovered high cancer risks particularly among people 40% or more overweight.



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Keats, Socrates and Fool's Parsley—Water Hemlock Poisoning

Ronald B. Mack, M.D.

ALL right Mack, this time you have gone too far. Socrates and hemlock, OK, but not Keats. You are really pushing it boy!!

To my detractors let me just say — a pox on your house!! John Keats, after all, was a "brother" and he did write a poem referring to the hemlock. That's right — he was a doctor. No, he did not graduate from Bowman Gray or Duke or Loyola or even the University of Texas, but he did devote five years of his life to studying medicine — 4 years as an apprentice to the apothecary-surgeon Thomas Hammond and 1 year at Guy's and St. Thomas' hospitals in London. While a student, he began to write poetry and at the age of 21 years, in 1816, he chose poetry as his profession instead of surgery (the DRGs must have really been tough back then). Don't you envy him, just a little?

John Keats is considered one of the greatest poets in the English language. His most beloved poem is thought to be "Ode To A Nightingale" which begins, as you remember so well, "My heart aches, and a drowsy numbness pains my sense, as though of hemlock I had drunk. . . ." Apparently Keats kept his medical texts and wove medical and scientific ideas into his poetry. He continued, even as a poet, to diagnose and treat his friends' maladies (he was fully licensed). Alas, he could not save himself, however, and died in 1821 at the age of 26 years of tuberculosis. He is buried in Rome and hard by the Spanish Steps in that beautiful city is a marker on the door of the dwelling in which he spent the last part of his short, productive life. He was, after all, the classic example of an oxymoronic poet (enough of that — it is shameful to speak of the dead in such a derogatory manner). No, no, no — *oxymoron* is the Greek word for a phrase that unites two contradictory ideas in a single meaningful term, e.g., delightful IRS agents.

The poisons we are discussing today are part of the same family that brought you celery, parsnip, parsley and carrots. The bad members of the family are the hemlock brothers (poison and water) and Fool's parsley. All three of these beauties are potentially fatal if ingested but the *water hemlock* (Cicuta maculata) is considered by the experts to be the most dangerous and, in fact, just may be the most poisonous plant in North America. In order for me not to get confused I am going to limit most of my remarks to this plant. But first a disclaimer — the plant known to many, many people as hemlock is in fact the hemlock tree, which is *harmless*.

The water hemlock, AKA beaver poison, cowbane, poison parsnip, etc. is approximately three to seven feet tall with quite distinctive roots and stems. The lower stem is usually thick and joins to a multiple root that resembles a bunch of carrots. When the stem is cut a yellow oily sap extrudes (Ugh!!) which has the odor of raw parsnips. At least the flowers are pretty; small, white, heavily scented flowers which grow in umbrella-like clusters known as umbrels. This plant usually grows only in wet areas such as marshes, swamps and creek banks.

The entire plant is poisonous and not suitable for human consumption but the roots are the most poisonous sections. These roots resemble parsnips or wild carrots and are mistakenly picked by the unwary to eat. The toxic ingredient is an unsaturated aliphatic alcohol called *cicutoxin*. One bite-sized piece of the root can kill an otherwise healthy adult; a piece of root the size of a walnut can kill a cow and a single root has been known to do in a horse. The hollow stems can be used to construct whistles, which have caused death in children — we are talking dangerous plant here.

If you accidently chew this stuff up and swallow it, within 15-60 minutes you get very nauseated, with increased salivation and emesis. Many patients describe a burning sensation in the mouth and dysphagia. Tremors can occur in this initial phase of the poisoning. Then severe abdominal cramps and violent emesis ensue as well as diarrhea and this is the good news because the emesis can remove any material from the plant remaining in the upper gastrointestinal tract. The bad news is that seizures occur in this phase and these are probably best described as severe with violent clenching of the teeth, intense muscle spasms, convulsions that are grand-mal like and opisthotonus. At this point the victim is usually unconscious, the pulse is slow and weak and respiration is depressed. Delirium is very common in those still conscious. Death from cardiorespiratory failure can occur as early as 15 minutes post ingestion or as late as 8 hours after eating the plant. The pupils are typically dilated but my pupils got dilated by merely reading about this horrible flora. Needless to say, you would expect the CPK to be elevated after all this jumping around and it is. You need to observe the patient for myoglobinuria. Some impairment of mentation can be seen in survivors. It is of interest that the principal plant in the United States responsible for producing convulsions as the primary toxic event is the water hemlock.

The treatment of the poisoning that results from this extremely dangerous plant is symptomatic — no magic antidote here. If vomiting has not already occurred by the

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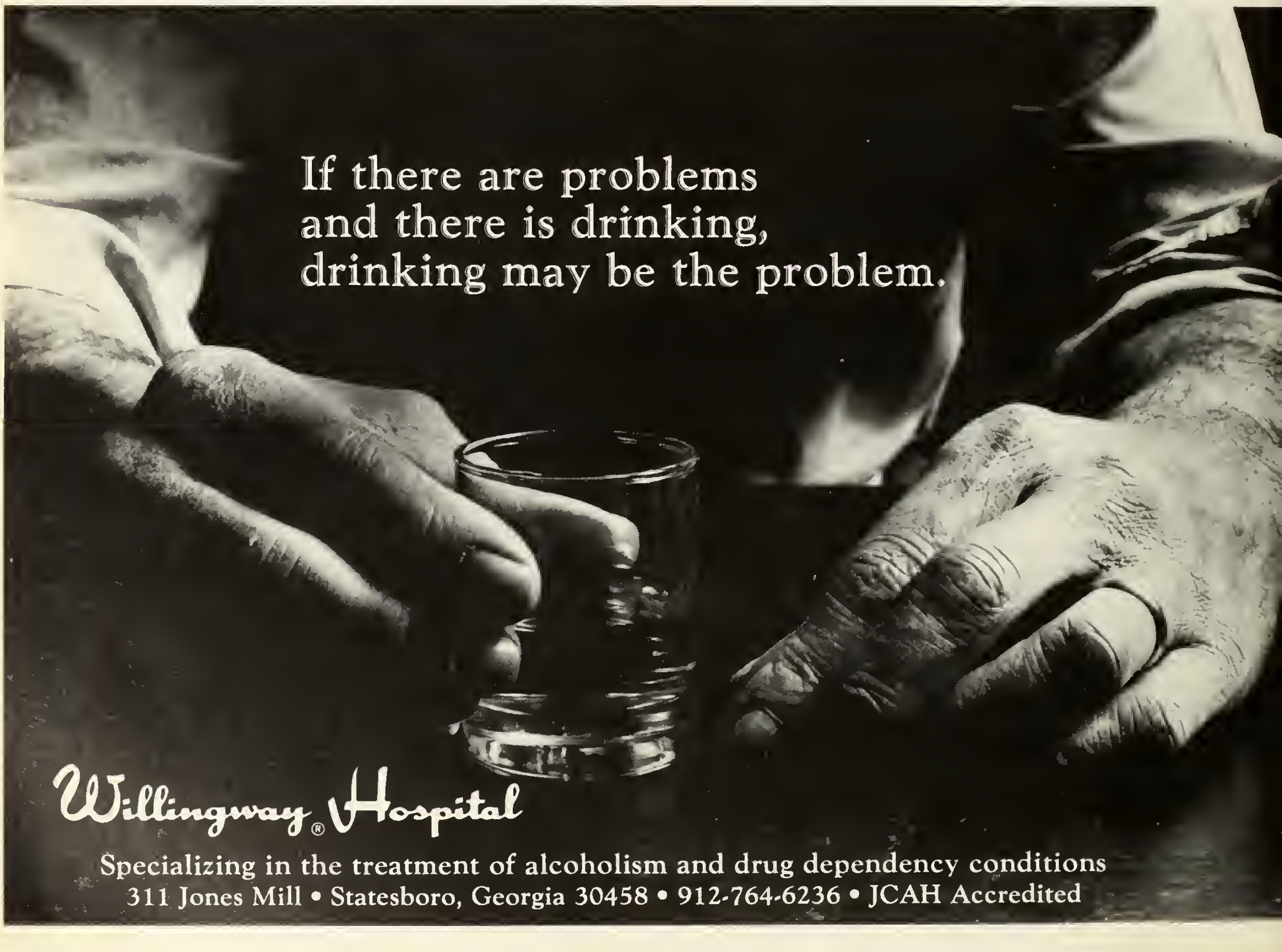
From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

time you are consulted (unlikely in view of its very irritative effect on the GI tract and rapid onset of action) and if the patient is alert, gastric emptying via ipecac induced emesis can be performed. The big challenge therapeutically is the cessation of the seizures and rapidly acting intravenous anticonvulsants seem to be the way to go. Many authors prefer parenteral diazepam (Valium) for this purpose; others prefer intravenous barbiturates such as thiopentone sodium. The constant seizure activity can cause an outstanding metabolic acidosis for which sodium bicarbonate may be required. Some authorities maintain that the spasms and convulsions that occur in this poisoning are the most violent they have ever seen with any disease.

Well, how about Socrates? That's what I say, how about Socrates? If the truth were known he did die from drinking hemlock but it was *poison hemlock*, not water hemlock. This plant is a common weed that grows up to eight feet tall and is found in waste areas of our country. It was apparently popular in ancient Greece as a method for inducing death by suicide, homicide, execution, etc. Reported instances of severe poisonings in this country from poison hemlock are quite uncommon; the Greeks on the other hand were apparently quite happy with its lethal qualities. Socrates was about 70 years old in 399 B.C. when he was executed for corrupting the youth of Athens. What he actually taught was hardly corrupting or seditious — he merely taught that students should doubt undocumented statements and that ideas should be clarified by means of rational answers to rational questions. One of his better dictims was "an unexamined life is not worth living." Heck, I say that all the time; well I didn't say it yesterday, but. . . .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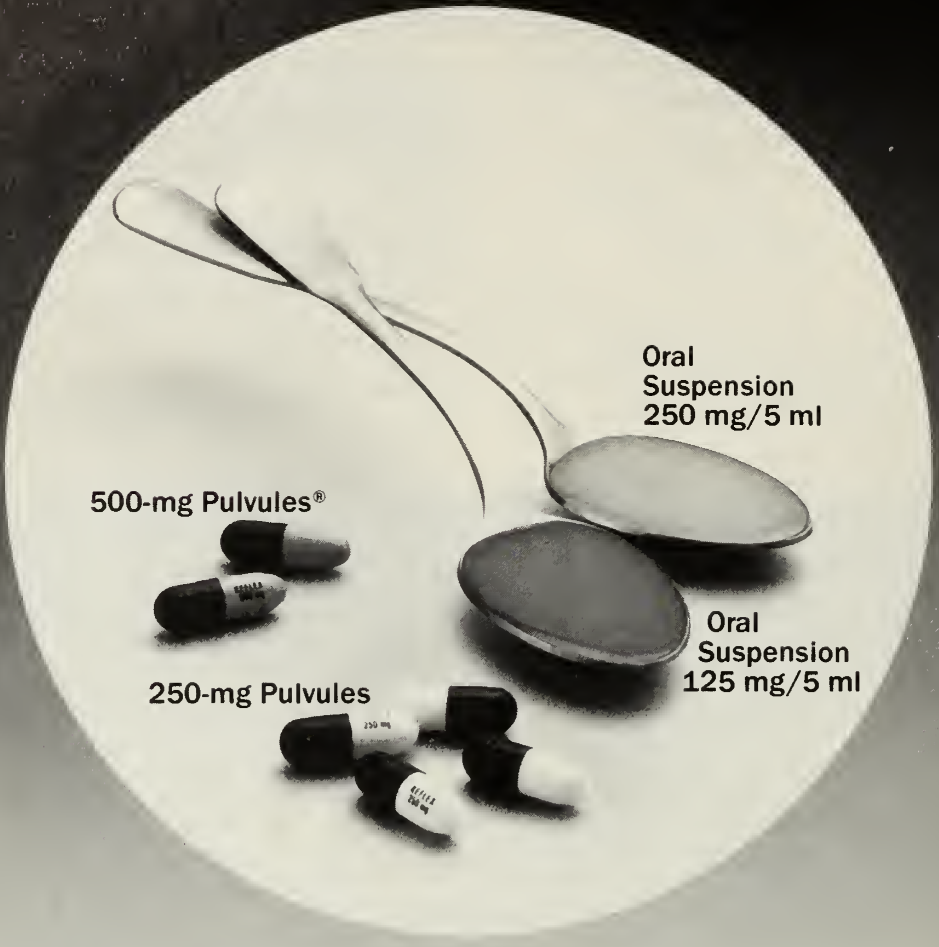

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Why an Army Medical Reserve?

W. Grimes Byerly, M.D.

IN the last several years any monthly issue of the *North Carolina Medical Journal* will contain three, four, or five full page advertisements from the Army, Navy and Air Force with the purpose of interesting physicians to join either the Active Component or Reserve Component Medical Corps of the various services.

At the annual meeting of the North Carolina Medical Society there are always two or three booths dedicated to military medical recruiting.

For approximately five years the United States Army has dedicated an individual officer recruiter to the State of North Carolina. His sole job is to recruit physicians for active duty Army Medical Service and assist the Medical Reserve forces in the State in their recruiting efforts.

The need for physicians in the military has existed from the beginning of our nation, and various techniques have been employed over the years to meet this need. With the advent of the Second World War, the general ground swell of patriotism and the intellectual knowledge that physicians were needed, the country achieved its necessary military medical personnel without a great deal of difficulty.

Major General Leonard Wood in 1916 wrote, "Behind the Regular Army must always stand the great Reserve Army consisting of the able-bodied men of the nation, so trained as to be promptly available for military service as needed but following their normal occupations in times of peace."

As a matter of history, the entire Reserve structure of the American Military was begun with the passage of Senate Bill 1424 on the 23rd of April, 1908, which authorized the Secretary of War to establish an Army Reserve Corps of Medical Officers who could be ordered to active duty in the time of emergency. Within a year over 300 men had been commissioned into the Medical Reserve Corps including such distinguished persons as Dr. Roswell Park, the surgeon who had attended President McKinley, and Dr. Wythe and Dr. Bryan, former Presidents of the American Medical Association.[1]

There has never been a tradition of a large peacetime standing Army or for that matter even a large Reserve force. During a time of crisis or war the mobilization of the untrained civilian community was the method the United States used to achieve a large military force. Until the close of the Second World War, the United States had always been allowed the luxury of time to produce the weapons and men necessary to fight its wars. Following the close of World War II, with the fact that the burden of Western societal defense militarily would fall increasingly on the United States and the luxury of time and distance would not be available, the American military had to restructure itself along with the consensus and direction of the American public as to how large a standing Army and standing Reserve force are both needed and allowable.

As is well known following the Second World War, the military physician supply was kept in a correct posture at least numerically, with the use of the civilian draft. Although the medical profession occasionally cried out its discomfiture because of the double jeopardy placed upon physicians in having to potentially serve their military obligations as non-physicians and then repeat it later on as a doctor, the situation continued to exist until the early 1970s.

The present problems and challenges of the Army Medical Reserve more or less began when President Nixon campaigned on a theme of ending the draft in 1968. During the years of winding down the Vietnam War, President Nixon directed (former) Secretary of Defense, Thomas S. Gates, Jr., to develop a comprehensive plan to eliminate conscription and establish an all volunteer force. The Gates Committee reported out in February 1970 that the all volunteer force should be just that and not a mixed force of conscripts and volunteers. The emphasis was upon the active force with little attention paid to the reserve components because a lack of data made it difficult to assess the impact of the volunteer army upon the Reserves. Concomitant with this the Army Chief of Staff, General William C. Westmoreland, issued a memorandum establishing that the reserve components must be considered the initial and primary source of additional units and individuals in any future rapid mobilization and directed Army planning predicated on this concept.[1] In the fall of 1970 the Army scaled down on withdrawal from Vietnam. To accomplish the reduction in size, units with service and support capabilities were removed from active duty and placed in the reserve structure. Money required for modernization was saved. With the abolition of the draft and the attempt to attain a volunteer army, a disastrous decade followed for the Army Medical Corps and in particular the Reserve Medical Corps.

As the civil unrest of the late 1960s stimulated a political decision to go to the all volunteer force, the fiscal realities of the early 1970s prompted the Army's total force policy. The reservist receives approximately 15% of the pay of an active duty soldier and, likewise, reserve units have lower operational and maintenance costs. It is estimated that the cost of maintaining approximately 500,000 reservists in the Ready Reserve is approximately one-tenth of that of main-

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From Byerly Surgical Associates, 24 Second Avenue, N.E., Hickory 28601.

Dr. Byerly serves his country as Col. Wesley G. Byerly MC USAR, Commanding Officer, 3274 USA Hospital, Durham, NC.

taining a similar number of men and women on active duty.

In an excellent and just recently published book on the history of the Army Reserve, the authors have presented a convincing case for the Reservist being *Twice the Citizen*.[1] Our country can no longer fight wars with minutemen militia picking up their muskets and marching off to a battle a few hundred miles away to be sustained by the local economy. The complexities of modern warfare require that those who fight in whatever manner, be it the use of the rifle, the typewriter, the x-ray machine, the computer, or whatever, be trained at the moment they begin their service and know exactly how to fit into the pattern of useful service from the start. We know that the tools of war are different and we know that wars will be "come as you are." For that reason an Army Medical Reserve instantly available is a vital necessity for the care of the injured of our future battles and wars.

Nearly two-thirds of the Army field hospitals and more than 40% of non-hospital medical units are manned by Army Reservists. Of all the military skills that are needed most after mobilization, the most difficult to recruit and retain are those of the varied medical specialties.

Phrased in another way, the fact that 66% of the active Army's medical assets and support are in the Reserve structure points up the absolute necessity for maintaining an adequate Reserve! The dependence by the Army on the Reserve to perform this mission makes obtaining professional medical people an immensely important task. This dependence of the Army upon the Reserve structure is vital in the early 1980s and, indeed, Lt. General William R. Richardson in addressing the Association of the United States Army in October 1982 categorically stated that the Army's ability to fight a war without the Reserves was zero.

Encouragingly, there has been a significant growth in Reserve Army health care professionals. Nursing strength is up to more than 79% of authorized levels from barely half strength just five years ago. Our overall physician strength now stands at 62%, up from less than 30% just four years ago.

All major Army Reserve Medical Units are commanded by physicians who are commissioned as Medical Corps Officers in the Army Reserve. The units are located in and near most major cities in the United States and through organizational exchange and management a physician may be placed in one unit geographically far away and work and train and participate in another that is physically closer for him.

Specific questions such as rank at time of commissioning, the amount of pay, creditable years of service for retirement, etc., are outside the scope of this particular discussion. However, given all the needed information, the special AMEDD physician recruiters scattered throughout the United States and the Office of the Surgeon General can give definite answers to those questions.

What are the reasons a physician should consider participating in the Army Medical Corps Reserve Structure?

First and foremost is what I shall call the cadre system consideration. This is an amalgamation of several factors that involves dedicated groups of people who work in the system, learn how to live with it and learn to manage the system. Therefore, they are immediately available as managers when the system must be expanded rapidly. It goes without saying that our country will never go to war without medical support for the military. In almost any kind of mobilization, the total force will of necessity have to be expanded. Such an expansion would, of course, mean an increase in the total number of physicians. Physicians can be obtained in the same way as cooks and bakers and infantrymen. From a technical point of view, they would need very little training and could be put to work instantly. The biggest problem would be that of managing a large number of physicians. A cadre of managers for the Reserve would be essential.

A second reason for participation in the Army Medical Reserve can be the amalgamation of several financial considerations. The money paid for the weekend drill for most physicians, agreed, does not add up to what the ordinary physician would make during the same period of time. But the challenge is, would the physician be working that period of time anyhow? The retirement benefits after the achievement of what are called "twenty good years" has an accrued benefit over and above what the physician would place in a pension plan. My query and challenge is, would the same physician put that *much more* aside for a retirement?

Other reasons for the consideration of the Army Medical Corps Reserve include the fact that, as a physician, one is able to practice medicine and practice as he does in his civilian field. The days of sitting in a dreary armory looking at old movies on veneral disease or listening to some sergeant talk about infantry tactics are gone. Physicians in the Army Reserve who practice medicine (that is, those not in administrative positions) are truly able to practice medicine in a military setting at military and veterans hospitals.

Another consideration for the Army Medical Corps Reserve is that it can be looked upon in terms of civic duty. Most physicians become involved in community life and service during their career. Instead of working and serving with a civic club such as the Kiwanis or participating with the Red Cross, one could look at service with the Army Medical Corps Reserve in the same light as civic duty.

For many physicians Army medicine in the Reserve presents a change of pace. Additionally, there are the fellowship and new friendships that are engendered over the years. Many good doctors, nurses, and health care people are in the Army Reserve. Many of these people have other interesting avocations and personalities, and getting to know them and developing friendships that last for years is also a stimulating factor

A final factor in the consideration of participation in the Army Medical Corps Reserve is that of patriotism, pure and simple. It is truly amazing the number of people who are patriotic and behave in such a manner. Indeed I have found not a few physicians, particularly those who have some close foreign background, to feel a patriotic desire to serve this country that has granted them freedom and unexcelled opportunities.

What is service like with the Army Medical Corps Reserve? There are various levels of participation.

The first and most active is the troop program unit (TPU). The physician soldier is a member of a specific unit organization and has a specific duty and his unit has a specific mission. Each month a weekend drill period consisting of sixteen hours during the weekend and a fourteen day period of annual training once a year is the basis of this Troop Program Unit. There are variations in the theme as to how this required duty is performed.

A second and less intense program is that of the Individual Mobilization Augmentee (IMA) in which a physician is assigned to a position in the Army Medical Corps to which he would be mobilized in the event of mobilization. The physician then spends two weeks on active duty in this particular function each year.

A final group is that of the Control Group in which there is minimum participation but the physician maintains his commission.

The world society we find ourselves in today is one of increasing shortages in competition for limited resources. There are multiple threats and differing global contingencies with little warning time anticipated. The national military strategy is shaped by the efforts to fulfill all these requirements of our country and today is characterized by a tremendous reliance on reserve components. The reserve components are no longer ''Forces in Reserve.'' They are adjunct forces, fully professional, totally integrated, and completely involved. ''The point has been reached where Reserves must have the same consideration as the active [components] — under most scenarios, an increasing proportion of the Reserves will mobilize, deploy and be employed along with not following the Active Army.''[2]

It is to this end that a dedicated, active, and integrated Army Medical Reserve structure is an absolute necessity.

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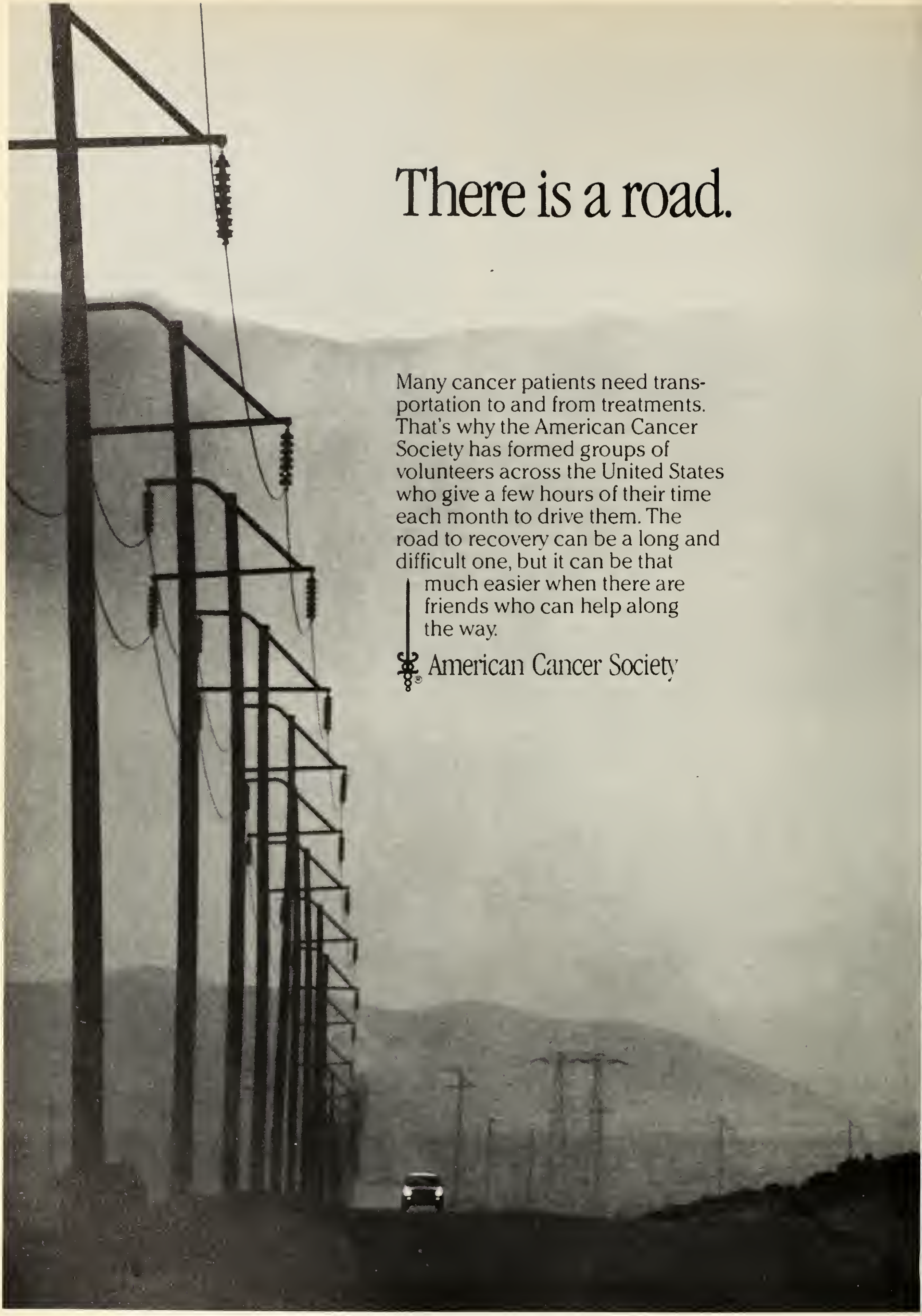
2. Sharp BF, Skipper DB. The reserve component dilemma: Mission versus time. *Military Review*. 1984;64:62-79.



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INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli, P. mirabilis, Klebsiella* species, and enterococci (*S. faecalis*).

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

Other antibacterial agents — Bacteriostats may interfere with the bactericidal action of cephalosporins in acute infection; other agents, e.g., aminoglycosides, colistin, polymyxins, vancomycin, may increase the possibility of nephrotoxicity.

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Carcinogenesis, Mutagenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential or mutagenesis.

Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 4 times the maximum indicated human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cephradine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

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Pediatric Use: Adequate information is unavailable on the efficacy of b.i.d. regimens in children under nine months of age.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported following use of cephradine: G.I. — Symptoms of pseudomembranous colitis can appear during antibiotic therapy; nausea and vomiting have been reported rarely. Skin and Hypersensitivity Reactions — mild urticaria or skin rash, pruritus, joint pains. Hematologic — mild transient eosinophilia, leukopenia and neutropenia. Liver — transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage. Renal — transitory rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others — dizziness, tightness in the chest, and candidal vaginitis.

DOSAGE: Adults — For respiratory tract infections (other than lobar pneumonia) and skin and skin structure infections: 250 mg q. 6 h or 500 mg q. 12 h. For lobar pneumonia: 500 mg q. 6 h or 1 g q. 12 h. For uncomplicated urinary tract infections: 500 mg q. 12 h; for more serious UTI, including prostatitis, 500 mg q. 6 h or 1 g q. 12 h. Severe or chronic infections may require larger doses (up to 1 g q. 6 h). For dosage recommendations in patients with impaired renal function, consult package insert.

Children over 9 months of age — 25 to 50 mg/kg/day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae*: 75 to 100 mg/kg/day in equally divided doses q. 6 or 12 h but not to exceed 4 g/day. Dosage for children should not exceed dosage recommended for adults. There are no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

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Cefuroxime Sodium

Austin Lee, Pharm.D.

Introduction

CEFUROXIME (Zinacef-Glaxo, Inc.) is a second generation cephalosporin recently approved by the FDA for use in the United States. Since its release in the late 1970s, cefuroxime has become the most commonly prescribed cephalosporin in the United Kingdom and Europe.[1] This review will familiarize the clinician with yet another cephalosporin antibiotic. Areas to be covered include the pharmacology, clinical trials, adverse reaction profile, and dosage and administration of cefuroxime.

Chemistry and Pharmacology

Cefuroxime is a semisynthetic cephalosporin antibiotic synthesized from cephalosporin C.[1] This drug shares its 7-aminocephalosporanic acid nucleus with other cephalosporins.[2] Chemically, cefuroxime is 6R, 7R-3-carbamoyloxymethyl-7(2Z)-2-methoxyimino-(fur-2-yl)-acetamido-ceph-3-em-4-carboxylate.[1] Like other cephalosporins, cefuroxime exerts its bactericidal effect on cells by interfering with bacterial cell wall synthesis.[2, 3] It inhibits the action of transpeptidase and carboxypeptidase enzymes, which are necessary for cell wall biosynthesis, resulting in either bacterial cell lysis or filamentation.[3-5] The effects of differing inocula size, media, pH, and addition of serum on the results of *in vitro* sensitivity testing have been evaluated; the latter three factors produced no appreciable effects,[4-8] and most studies have failed to demonstrate a significant inoculum effect.[4-8] However, appreciable increases in minimum inhibitory concentrations (MIC) secondary to increases in inoculum size have occurred with some strains of bacteria.[8] Concentrations required to inhibit 90% of isolates (MIC_{90}) are listed in table 1.

Pharmacokinetics

Cefuroxime is poorly absorbed following oral administration. Urinary recovery is only 1% after a 1.0 g oral dose.[9] Therefore, cefuroxime is commercially available for parenteral use only. The manufacturer reports that development of an oral form of cefuroxime is in progress. Intravenous (IV) infusion over 30 minutes produced peak serum levels of 37.8 mcg/ml after a 500 mg dose and 51.1 mcg/ml after a 750 mg dose, whereas IV infusion of 750 mg, 1.5 and 3.0 g over 1 hour led to peak serum levels of 38.0, 64.4, and 98 mcg/ml, respectively.[10, 11] After a bolus IV injection given over a period of 3 minutes, mean peak serum concentrations were about 42-66 mcg/ml after a 500 mg dose, 53-73 mcg/ml after a 750 mg dose, and 105-151 mcg/ml after a 1.5 g dose.[9, 12-14] The apparent volume of distribution following IV injection was 9.3-12.8 L/1.73 m^2, which corresponds to the extracellular volume.[9, 15] This follows the pattern of distribution of other cephalosporins.[16] Binding to human serum protein is 33-41% and is notably less than that of other cephalosporins.[7, 9, 16] The elimination half-life generally ranges from 60-77 min.[11, 15] Urinary excretion of unaltered cefuroxime usually accounts for over 95% of each dose, and no significant metabolites have been detected.[9] Most of the dose is excreted in the first six hours, and almost all is accounted for in a 24-hour urine collection.[9, 12] Average urine levels of 500-2000 mcg/ml were present 1-2 hr after 250-500 mg, and 1000-7000 mcg/ml was present after 750 mg and 1.0 g doses.[9] Renal tubular secretion is responsible for 43-54% of cefuroxime renal elimination, as has been confirmed by administration of oral probenecid.[9]

After intramuscular (IM) injection, peak serum levels attained at 0.5-1.0 hr after administration ranged from 14.8 mcg/ml after 250 mg, 24.8-25.7 mcg/ml after 500 mg, 27-34.6 mcg/ml after 750 mg, 32.2-40 mcg/ml after 1.0 g, to 46 mcg/ml after 1.5 g.[9, 13, 17] Serum concentrations were maintained at detectable levels for 8 hours at all dosages except the 250 mg dose.[9] The serum half-life ranged from 65 to 82 min.[9] Mean urinary recovery was at least 95% of the dose.[9] The total amount of drug available is the same for equivalent doses given IM or IV based upon

Table 1
Concentrations Required to Inhibit 90% of Isolates (MIC_{90})[5, 6, 8]

Organisms	Cefuroxime mcg/ml	Cefamandole mcg/ml
S. aureus (unspecified)	0.8-1.6	0.2-0.8
S. epidermidis	0.12-4.0	0.12-2.0
S. faecalis	> 64	> 32
S. pneumoniae	0.006-0.01	0.03-0.06
N. gonorrhea	0.12-0.25	1-2
H. influenzae	0.25-0.5	0.25-0.5
E. coli	6.2-12.5	6.2-12.5
Klebsiella spp.	1.6-3.1	12.5-25
Enterobacter spp.	200-400	200-400
Citrobacter spp.	6.2-12.5	< 0.8
Providencia spp.	200	100
Proteus spp.		
Indole-negative	1.6	3.1
Indole-positive	> 400	25-100
Pseudomonas spp.	16- > 32	32-> 32
Serratia spp.	> 400	> 400
Acinetobacter spp.	> 400	200-400
B. fragilis	> 64	16-32

From the Department of Pharmacy, Duke University Medical Center, Durham 27710.

area under the concentration-time curve.[9] Cefuroxime distributes into many body tissues and fluids.[3] Numerous studies in neonates, children, and adults with meningitis have documented its penetration into cerebrospinal fluid (CSF). Penetration has correlated with the degree of meningeal inflammation.[18, 19] The mean CSF levels in these studies have ranged from 2.4 to 10.3 mcg/ml and have been considered adequate for treatment of meningitis caused by susceptible pathogens.[18, 20-25]

Elderly Patients. A pharmacokinetic study conducted in 40 elderly patients (mean age 77.5 years) concluded that dosage and dosage intervals should depend upon renal function rather than upon age.[26] Therefore, the guidelines for dosing in the normal adult patient should be followed.

Neonates and Infants. Neonates less than 3 weeks old (average 4.2 days) exhibited a half-life of approximately 275 minutes after a 10 mg/kg IM dose.[20] The half-life was age-related and ranged from 240 minutes in 14 day-old to 338 minutes in 1 day-old infants. Peak serum levels ranged from 18.6 to 25.6 mcg/ml and showed a slight dependency on body weight. Urine excretion accounted for 53-87% of each dose and urine levels were 10-fold greater than serum levels. Multiple 10 mg/kg doses given every 8 hours showed no evidence of drug accumulation if body weight was greater than 2,000 g. The investigators suggested twice-daily dosing with body weight less than 2,000 g. Another study observed a similar age dependency for cefuroxime elimination, with the half-life decreasing from 5.1 hr on day 1 of life to 1.9 hr on day 6 in neonates of greater than 2.5 kg birthweight.[27] Neonates of less than 2.5 kg birthweight excreted cefuroxime more slowly. Mean peak serum levels ranged from 19.1 to 24.5 mcg/ml after 15 mg/kg and from 39.6 to 56.7 mcg/ml after 25 mg/kg IM doses. These investigators also suggested a twice-daily dosing schedule in neonates with birthweight less than 2.5 kg. Infants and children aged 3 weeks to 2 years (average 6.5 months) and ranging in weight from 2,800 to 9,500 g (average 6,500 g) were also studied.[28] After a 15 mg/kg IM dose, the peak serum level was 26.6 mcg/ml at 0.5 hr with a serum half-life of 63.8 min. Intravenous administration of 12 mg/kg produced a peak serum level of 30 mcg/ml. Half-lives in these older children were similar to those observed in adults.

Patients with Impaired Renal Function. Cefuroxime excretion is reduced by renal failure. Half-lives have been determined for varying degrees of creatinine clearance (Cl_{cr}), (see table 2). Cefuroxime levels achieved in peritoneal dialysate ranged between 15 and 20 mcg/ml.[29] Cefuroxime has been added to peritoneal dialysate of patients on continuous peritoneal dialysis in a final concentration of 200 mg/L for 6 cycles/day.[30] The mean dialysate level was 26 mg/L in effluent and 18 mg/L in serum at the end of the first exchange. Dosage guidelines for cefuroxime are based upon the fact that significant accumulation does not occur until Cl_{cr} is less than 20 ml/min.[31] Dosing guidelines based upon Cl_{cr} are listed in table 3. Patients on hemodialysis should receive a 500 mg loading dose post-dialysis.[32]

Clinical Trials

The Food and Drug Administration has approved the use of cefuroxime for the treatment of serious infections caused by susceptible strains of specific microorganisms in the following diseases: 1) lower respiratory infections, 2) urinary tract infections, 3) skin and skin structure infections, 4) septicemia, 5) meningitis, and 6) uncomplicated gonorrhea and disseminated gonococcal infections.[3] Few published comparative trials are available for evaluation of cefuroxime. Most of the available clinical data are derived from non-comparative open trials designed to evaluate the safety and efficacy of cefuroxime.

Table 2
Determination of Cefuroxime Half-life ($t_{1/2}$) Based upon Creatinine Clearance (Cl_{cr})[29]

Cl_{cr}(ml/min)	$t_{1/2}$ (hours)
> 80	1.05
50-79	1.03
25-46	2.55
10-24	5.05
< 10	14.8
anuria (no dialysis)	21.9
on hemodialysis	3.75
on peritoneal dialysis	13.6

Table 3
Cefuroxime Dosing Guidelines Based Upon Creatinine Clearance (Cl_{cr})[3]

Cl_{cr}(ml/min)	Dose	Frequency
> 20	750 mg-1.5 g	q8h
10-20	750 mg	q12h
< 10	750 mg	q24h

Lower Respiratory Tract Infection. Cefuroxime's antibacterial spectrum encompasses *S.pneumoniae, H. influenzae, S. aureus,* and *Klebsiella* sp., the bacteria most likely to cause pneumonia. Furthermore, because of its stability to the beta lactamases of *S. aureus* and *H. influenzae,* it provides a broad coverage for pneumonia. Two large non-comparative trials (total 464 patients) have assessed cefuroxime 750-1000 mg IM q8h for lower respiratory tract infections.[34, 35] The response rates were 88-90% for bronchopneumonia, 89-97% for exacerbation of COPD, 69% for postoperative pneumonia, 86% for bronchitis, and 86% for pneumonia secondary to cancer obstruction. Other non-comparative studies of cefuroxime in the treatment of adult respiratory tract infection have revealed cure rates ranging between 90-100% after regimens of 750 mg-1.5g IM or IV q8-12h.[36-38] Cefuroxime 25 mg/kg IV or IM q8h has also been an effective treatment for pneumonia in 100 infants and children.[39] Dosages of 15 mg/kg q8h and 50 mg/kg q12h have provided adequate response in two other smaller trials in children.[40, 41]

Bone and Joint Infections. Data on clinical efficacy of cefuroxime in bone and joint infections are limited. In a series of 75 children with suppurative bone and joint infections, patients received either cefamandole or cefuroxime as their initial antimicrobial therapy.[42] Twenty-seven children received cefuroxime in doses of 15 mg/kg/day in three divided doses. Parenteral therapy was administered for a mean duration of five days (range 2-21 days). Therapy was completed with oral antibiotics, in most cases with either cefaclor or cephalexin. All patients showed clinical improvement while receiving cefuroxime, although one treatment failure was reported.

Cefuroxime may potentially be effective in the treatment of osteomyelitis and septic arthritis. However, its definitive role in these conditions has yet to be established and will require clinical trials with long-term follow-up for sequelae.

Gonorrhea. Lossick et al compared a single IM dose of 1.5 g of cefuroxime with 4.8 million units of procaine penicillin G, both combined with 1.0 g of oral probenecid.[43] Overall response was 96% for cefuroxime and 95% for penicillin. Similar success has been reported in non-comparative studies after treatment with 1.0 and 1.5 g cefuroxime with or without probenecid.[44, 45] Cefuroxime has been shown to have *in vitro* activity against beta-lactamase-producing strains of gonococci.[8] Cefuroxime has been used as a single 25 mg/kg IM dose in the treatment of gonorrhea in children with pharyngeal, rectal, and/or urethral disease.[46] Seventy-six percent were cured completely within 48 hours after treatment. The remainder had persistence of symptoms due to concurrent chlamydial infection.

Although a single dose of cefuroxime has proven effective in the treatment of uncomplicated gonococcal infection, it should be reserved for patients either allergic to penicillin or known to have strains of *N. gonorrhoeae* that produce beta-lactamase.

Meningitis. Ampicillin and chloramphenicol are currently recommended for initial therapy of bacterial meningitis in children. The emergence of ampicillin- and chloramphenicol-resistant strains of *H. influenzae* has stimulated the search for alternative forms of antibiotic therapy. The overall performance of first and some second generation cephalosporins in bacterial meningitis has been poor. A review by Gold et al of the results of studies on the degree of penetration of cefuroxime into the CSF in various disease states concluded that 1) the degree of CSF penetration of cefuroxime generally increases with the degree of meningeal inflammation, and 2) the degree of penetration is somewhat variable and shows no clear relationship to the time interval between antibiotic administration and sampling of the CSF.[2] Friedrich et al concluded that cefuroxime, like earlier cephalosporins, diffuses poorly into the CSF.[47] However, several reports have documented the efficacy of cefuroxime in the treatment of meningitis in adults and children.

A study conducted by a Swedish collaborative group supports the potential role of cefuroxime in the treatment of meningitis.[25] In a prospective, randomized study these investigators compared cefuroxime (60-75 mg/kg/dose q8h in 9 children, 3 g q8h in 11 adults) with a combination of ampicillin and chloramphenicol in 40 evaluable patients with culture-proven bacterial meningitis. Clinical isolates included *H. influenzae* (20), *N. meningitidis* (11), *S. pneumoniae* (5), *B. cattarhalis* (1), *S. aureus* (1), alpha-streptococcus (1), and *H. parainfluenza* (1). The response rates of 86% for cefuroxime and 74% for ampicillin-chloramphenicol were not statistically different, indicating that cefuroxime was at least as effective as combination therapy in this study.

Cefuroxime is approved for use in the treatment of bacterial meningitis.[3] Because of more potent antimicrobial activity and increased diffusion into the CSF, the third generation cephalosporins show greater promise for the treatment of meningitis than do the first two generations.

Urinary Tract Infection. Cefuroxime (which is a parenteral antibiotic) will probably have little role to play in the outpatient treatment of urinary tract infections. Hofstetter et al reported clinical cure or improvement in 21 of 26 patients treated with cefuroxime 2.25 g IV daily.[48] Fifteen of 29 strains of bacteria were eradicated. In a study of 40 patients (21 of whom had underlying urological conditions), 38 of the 40 original pathogens isolated were eradicated.[49] Treatment consisted of cefuroxime 500 mg IM q8h.

Hospital acquired infection in 34 geriatric patients with recurrent or chronic urinary tract infection was treated with cefuroxime 500 mg IM or 750 mg IM given three times a day for 7 days.[50] The original pathogen was eliminated in 7 of 16 treated with 500 mg doses and in 13 of 18 given 750 mg doses. Following treatment with cefuroxime 2-4 g daily, 14 of 22 patients achieved cures after having failed on other antibiotics.

Soft-Tissue Infections. Cefuroxime has proven effective in treating soft-tissue infections. Fifty-five children with soft-tissue infections were treated with cefuroxime.[51] Most children were treated with 50 mg/kg/day IV in 4 divided doses. Clinical results were good in 50, fair in 2, and unevaluable in 3. Adult doses of 750 mg every 8h and pediatric doses of 50 mg/kg/day divided into 3-4 doses should be used when the etiologic agent is a susceptible organism.[3] When the pathogen is almost certainly limited to gram-positive aerobic organisms, an antibiotic with a more narrow spectrum of activity should be used.

Bacteremia. Clinical studies have included small numbers of septic patients who have been successfully treated with cefuroxime.[52, 53] Cefuroxime was used for empiric coverage in 57 children with leukemia or solid tumor who developed fever while neutropenic.[54] The combination of cefuroxime plus gentamicin was effective in all cases. However, a list of pathogen and sensitivity data is absent; therefore, the merits of cefuroxime in this setting are questionable.

Surgical Prophylaxis. Cefuroxime's ability to achieve significant concentrations in most body fluids and tissues has provoked interest in its use for surgical prophylaxis. Cefuroxime provided effective prophylaxis in 69 total hip and 37 total knee replacements.[55] Patients received three 1 or 1.5 g IM doses at the time of surgery and 6 and 12 hours later. Comparison of cefuroxime and placebo in coronary artery bypass surgery showed no difference in the incidence of sternal or leg wound infection.[56] However, significantly fewer cefuroxime-treated patients developed postoperative pulmonary infection. This study has been criticized for the vague clinical criteria used to define complications; therefore, interpretation of the results is limited.

In upper gastrointestinal surgery, patients receiving a single 1.5 g IV dose of cefuroxime prior to upper GI surgery showed a significant reduction in wound sepsis, abscess and septicemia when compared with controls.[57] Cefuroxime 1.5 g IV was used with or without metronidazole and also compared with placebo in rectocolonic, gastric, and small bowel surgery.[58] Cefuroxime-treated patients developed fewer infections compared with placebo, and more infection when compared with combination therapy. Cefuroxime was significantly better than placebo in prevention of infection after small bowel and gastric surgery. One study included 416 patients with acute cholecystitis and compared the prophylactic efficacy of three cephalosporins in preventing wound infections.[59] Patients received either 1 g cefazolin, 0.75 g cefuroxime or 1 g of cefamandole. The degree of decrease in wound infection rates with cefuroxime was not significantly better than that achieved with cefazolin or cefamandole. In a randomized double-blind study of 472 patients undergoing major elective gynecologic surgery, one group of patients received a single postoperative 1.5 g dose of cefuroxime, and the others received no antibiotics.[60] Results suggested that a single dose of cefuroxime reduced the frequency of postoperative pyrexia, urinary tract infections, and amount of antibiotic needed after surgery. However, cefuroxime's role in gynecologic prophylaxis may be hindered by its limited *in vitro* activity against *B. fragilis*. A combination of metronidazole and cefuroxime was associated with no postoperative wound infection in total abdominal hysterectomy, vaginal hysterectomy, pelvis floor repair, or salpingectomy.[61] Cefuroxime 1.5 g IV was compared with placebo for prophylaxis prior to transurethral resection of the prostate.[62] No urinary tract infections were reported for either group postoperatively.

Side Effects and Toxicity

Cefuroxime is well tolerated by adults and children. The most frequently encountered side effect is local irritation at the site of injection, which includes thrombophlebitis and transient pain after intramuscular injection.[3] Pain after intramuscular administration may be lessened by co-administration of lidocaine.[44] Rash, pruritis, urticaria, and positive Coombs test have been relatively uncommon.[3] Caution is advised when administering this agent to patients with prior allergic reactions to other beta-lactam antibiotics.[3] Gastrointestinal reactions such as stomatitis, nausea, and diarrhea occur infrequently. Transient elevations in liver enzymes are the most frequent laboratory abnormalities, but these have been clinically inconsequential. Clinical deterioration of renal function has not been observed, although elevations in blood urea nitrogen (BUN) have been reported. Patients with pre-existing renal disease have been treated successfully with cefuroxime with no apparent deterioration in renal function.[63] Hematologic abnormalities such as decreases in hemoglobin and hematocrit, eosinophilia, leukopenia, and neutropenia have been observed occasionally.[3] Pseudomembranous colitis, disulfiram reaction, and bleeding tendencies have not been reported during cefuroxime therapy.

Drug Interactions

The effects of oral administration of probenecid 500 mg 2 hours before and again 1 hour after IM injection of cefuroxime were studied in a cross-over study in 6 volunteers.[9] Concomitant probenecid increased serum concentration (30%) and serum half-life (32%), and decreased

Table 4
Dosage Guidelines for Cefuroxime Treatment[3]

Type of infection	Usual recommended dose
Adults (over 12)	
Uncomplicated UTI Skin and skin structure infection Uncomplicated pneumonia Disseminated gonorrhea	750 mg q8h IM or IV
Severe or complicated infections	1.5 g q8h IM or IV
Life-threatening infections Infections due to less-susceptible organisms	1.5 g q6h IV
Bacterial meningitis	up to 3.0 g q6h IV
Prophylactic use in clean-contaminated or potentially contaminated surgical procedures	1.5 g IV 30 to 60 min before initial incision, followed by 750 mg q8h IM or IV in prolonged procedures
Uncomplicated gonorrhea	1.5 g IM given as a single dose at two different sites, together with 1.0 g oral probenecid
Patients with renal insufficiency	See table 3
Infants and children over three months	
Mild to moderate infections	50 to 100 mg/kg/day in equally divided doses q6-8h
Severe or serious infections	100 mg/kg/day (not to exceed the maximum adult dose)
Bacterial meningitis	initially 200-240 mg/kg/day IV in divided doses q6-8h; may be reduced to 100 mg/kg/day IV on clinical improvement
Patients with renal insufficiency	modify frequency of dosage consistent with the recommendations for adults

apparent volume of distribution (20%) and renal clearance (40%).

Dosage and Administration

The usual dose of cefuroxime for urinary tract, lower respiratory tract, and skin and soft tissue infection of mild to moderate severity is 750 mg IM or IV q8h.[3] The dosage for severe infection of the urinary tract, respiratory tract, skin and soft tissue, and for sepsis is 1.5 g IM or IV q8h.[3] Life-threatening infections, including meningitis, are treated with 3 g IV q8h. A single 1.5 g IV dose immediately before surgery is recommended when cefuroxime is used for surgical prophylaxis.[3] A single 1.5 g IM dose plus 1 g of oral probenecid is efficacious in the treatment of gonorrhea.[3] In children more than 3 months old the usual dose is 50-100 mg/kg/day in equally divided doses, usually every 6-8 hours; however, initial doses of 200-240 mg/kg/day are recommended for meningitis therapy[3] (refer to tables 3 and 4 for general dosing guidelines and for patients with renal dysfunction). Cefuroxime may be given IV or by deep IM injection into a large muscle mass.[3] The IV route may be preferable for patients with bacterial septicemia or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance, particularly if shock is present or impending.[3] Intravenous injections may be given over 3-5 minutes as a bolus or as an infusion.[3] Cefuroxime is stable in most standard dextrose and saline solutions.[3] Solutions of cefuroxime, like those of most beta-lactam antibiotics, should not be added to solutions of sodium bicarbonate or aminoglycosides because of potential drug inactivation.[3] Cefuroxime has also been found compatible for 24 hours at room temperature when admixed in IV infusion with heparin (10 and 50 units/ml) in 0.9% NaCl injection, and KCl (10 and 40 mEq/L) in 0.9% NaCl injection.[3] As with other cephalosporins, however, cefuroxime solutions and suspensions tend to darken depending on storage conditions, without adversely affecting drug potency.[3]

Availability and Cost

Cefuroxime is available in 750 mg and 1.5 g vials. The average wholesale price is $5.88 and $11.70, respectively.[64]* At the Duke University Medical Center, daily patient cost is similar or lower for cefuroxime therapy when compared with cefamandole and cefoxitin (when comparisons are based upon manufacturer's recommendations for moderate-severe and life-threatening infections).

Summary

Cefuroxime is a new beta-lactamase-stable cephalosporin with a second generation antimicrobial spectrum similar to that of cefamandole. This new agent is efficacious and offers certain advantages over cefamandole. Cefuroxime has the advantage of a longer dosing interval (q8h), lack of bleeding abnormalities, usefulness in pediatric infections, long history of experience in Europe, and possibly a lower cost for therapy.

References available from the NCMJ editorial office.

* Prices quoted reflect the average wholesale price as published in *Redbook* or the quoted manufacturer's wholesale selling price.

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LEARNING WITHOUT WORDS

Pericardial Pseudoeffusion Due to Steroid-Induced Lipomatosis

Cynthia D. Mulrow, M.D. and G. Ralph Corey, M.D.

A chest radiograph showing cardiomegaly, a ''water bottle'' heart or the epicardial fat pad sign usually connotes a pericardial effusion. In recent years ultrasonography has been used to confirm this diagnosis. Unfortunately, echocardiography cannot differentiate between fluid and adipose tissue. We present a case of suspected pericardial effusion in which an awareness of the possibility of steroid-induced intrathoracic lipomatosis would have led to computerized tomographic scanning and prevented surgical exploration.

Case Report

A 47-year-old man developed a pruritic, eczematous rash on his left lower leg after taking hydrochlorothiazide for mild hypertension. Despite stopping the thiazide, the rash progressed; systemic steroids were used and the rash improved. Over a six month period multiple attempts to taper the steroids resulted in severe flares of the rash, and the patient was admitted for evaluation.

Serological tests for collagen-vascular disease, venography, and computerized tomographic scans of the abdomen and left lower leg were negative. When we decreased the steroid dose the patient developed nausea, dyspnea, and tachycardia. While breathing room air his arterial pH was 7.50, pCO_2 23 mm Hg, and pO_2 65 mm Hg. His chest radiograph (figure 1) revealed cardiomegaly and a prominent mediastinum. A ventilation perfusion lung scan was negative.

Diuretics (given for presumed volume overload) resulted in a blood pressure drop from 140/90 to 110/80 and a rise in pulse rate from 100 to 130. He had a pulsus paradoxus of 18 mm Hg. He stabilized when given fluids.

An echocardiogram (figure 2) was interpreted as showing a large pericardial effusion and a thick pericardium with ''stranding'' suggestive of a malignant process. A diagnostic pericardiectomy was undertaken but no pericardial effusion was found; the pericardium appeared normal except for an unusually large amount of pericardial fat. Pathological examination revealed normal pericardium with excessive but normal adipose tissue. The patient recovered from surgery without complications. The steroids were eventually tapered without recurrence of the rash. The etiology of his rash and systemic symptoms was never firmly established.

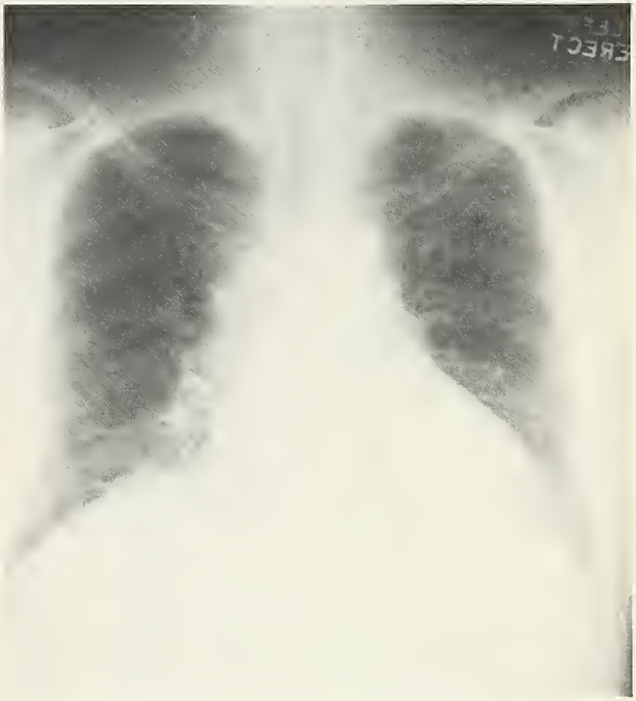

Figure 1. *Chest radiograph revealing cardiomegaly and a prominent mediastinum.*

Discussion

Increased truncal fat deposits, including intrathoracic fat deposits, occur in patients with endogenous[1] or exogenous[2] steroid excess. Most patients have other clinical characteristics suggestive of Cushing's syndrome, but it is sometimes difficult to distinguish pericardial fat deposition from more serious conditions such as neoplastic effusions. A history of long-term steroid use (usually more than 30 mg prednisone daily) is helpful. Excess fat may be noted in truncal, facial and supraclavicular areas. Chest radiographs commonly reveal symmetrical mediastinal enlargement, but pericardiac masses and generalized enlargement of the cardiac silhouette can be seen. The fat shadows are often poorly defined and not as dense as other superior mediastinal masses such as thymoma or lymphoma. Compression effects on the trachea or ribs are not seen.

Diagnosis of mediastinal lipomatosis depends on clinical suspicion, the use of computerized tomographic scanning[3] and occasionally on invasive procedures such as needle biopsy or thoracotomy. However, in patients with presumed pericardial effusion, echocardiography is the most

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From the Division of General Internal Medicine, Duke University Medical Center, Durham 27710.

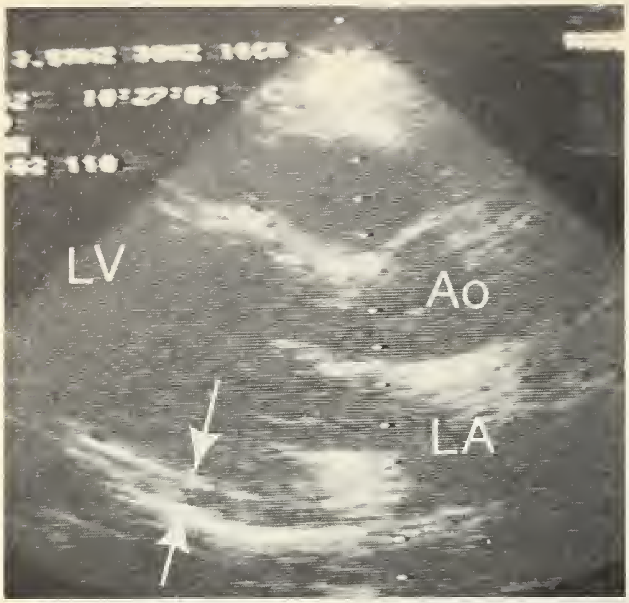

Figure 2. *Left parasternal long axis echocardiogram showing pericardial effusion (between arrows). Ao = Aortic root; LV = Left ventricle; LA = Left atrium.*

commonly used noninvasive diagnostic tool. Known drawbacks to this procedure include false positive diagnoses of pericardial effusions in patients with pericardial neoplastic disease.[4]

Our patient had a pericardial pseudoeffusion secondary to corticosteroid-induced pericardial fat deposition. Although pericardial pseudoeffusion is not a common occurrence, computerized tomography can usually distinguish low density adipose tissue from pericardial fluid or higher density tissue such as myocardium or tumor.[4] In particularly difficult cases tissue biopsy may be necessary.

Since increased cardiac and mediastinal adipose tissue does not appear to cause clinical dysfunction, there is generally no need for therapy.[2] Excess adipose tissue regresses after removal of the steroid stimulus.

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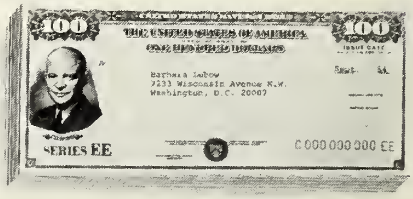

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IN STATE

March 13
Essentials of Ophthalmology and Otolaryngology for the Primary Care Physician
Place: Charlotte
Info: Martin J. Kreshon, M.D., 1600 East Third Street, Charlotte 28204. 704/372-3300

March 20
Pulmonary Embolism — Acute Care and Prevention
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

March 21-22
Current Cancer Research — Springboards for the Future
Place: Chapel Hill
Credit: 10 hours Category I AMA-PRA
Info: Pam Upchurch, Lineberger Cancer Research Center, UNC, Chapel Hill 27514. 919/966-3036

April 2
Physicians, Their Families and Stress — How to Survive in 1985
Place: Greensboro
Info: David M. Kaplan, M.D., P.O. Box 220, Summerfield 27358.

April 11
The North Carolina Neuro-Ophthalmology Review
Place: Chapel Hill
Credit: 4 hours Category I AMA
Info: Baird S. Grimson, M.D., 617 Clinical Science Building, 229H, UNC, Chapel Hill 27514. 919/966-5296

April 13
Neurosciences Update
Place: New Bern
Info: William B. Hunt, Jr., M.D., Box 2157, New Bern 28560. 919/633-8607

April 15-June 7
Postgraduate Course in Medical Sonics
Place: Winston-Salem
Credit: 35 hours Category 1 AMA per week
Info: James F. Martin, M.D., Center for Medical Ultrasound, Bowman Gray School of Medicine, Winston-Salem 27103. 919/748-4505

April 17
The Back — From Thoracic to Sacral
Place: Sanford
Credit: 2 hours Category 1 AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

April 24
Current Concepts in Otolaryngology for the Primary Care Physician
Place: Chapel Hill
Fee: $50
Credit: 6.5 hours Category 1 AMA, AAFP
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

April 25-27
New Expanded Advanced Cardiac Life Support Provider Course
Place: Asheville
Credit: 24 hours Category 1 AMA and ACEP and AAFP
Fee: $300
Info: Daniel L. Dolan, M.D., MAHEC, 501 Biltmore Avenue, Asheville 28801-4686. 704/258-0881

April 27
Rehabilitation of the Cancer Patient
Place: Chapel Hill
Info: Deitra Lowdermilk: 919/966-5390

May 1
The Pregnant Therapist
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-3571

May 3-4
House Officer Selection
Place: Chapel Hill
Fee: $325
Credit: 12 hours Category I AMA
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

OUT OF STATE

March 16
Reconstructive Plastic Surgery
Place: Richmond, VA
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 29-31
Ophthalmology: Cataract Surgery and Intraocular Lenses
Place: Williamsburg, VA
Fee: $275
Info: Kay Parrott, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 12-14
Third Annual Symposia on Anesthesia for Ambulatory Surgery
Place: Williamsburg, VA
Fee: $250
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 18-20
Radiology Review
Place: Hilton Head Island, SC
Fee: $350
Credit: 15 hours Category I AMA
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

April 19-21
Seventh Annual Conference on Emergency Medicine for the Primary Care Physician
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-27

Twentieth Annual Pediatric Springfest
Place: Williamsburg, VA
Fee: $235
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-28

Annual Meeting, Virginia Society of Otolaryngology-Head and Neck Surgery
Place: Irvington, VA
Info: Donna Strawderman, 4205 Dover Road, Richmond, VA 23221. 804/353-2721

May 3-5

Fifth Annual Clinical Concerns in Primary Care
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

May 10-12

Fifth Annual Radiation Oncology Course
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In Memoriam

Robert Wefer Williams, M.D.

Dr. Robert Wefer Williams died December 15, 1984 in Wilmington after a long illness. He was born in New York City on January 27, 1921, the son of Elsie Wefer and Robert Jay Williams. After graduating from Phillips Exeter Academy and Harvard College, he attended Cornell University Medical College, graduating in 1945. He was an Army-Air Force Flight Surgeon in occupied Germany from 1946 to 1948.

Following his honorable discharge as a Major from the Air Force in 1948, he worked at the Strang Clinic of New York Memorial Hospital. He then served a surgical residency at the Bowman Gray Medical School. Practicing as a general and thoracic surgeon in Wilmington from 1953 to 1978, he was especially recognized for his surgery on infants and children, much of which was done at the Babies Hospital in Wrightsville Beach.

Dr. Williams was a Fellow of the American College of Surgeons, a diplomate of the American Board of Surgery, and an early diplomate of the American Board of Thoracic Surgery.

He is survived by his wife, Isabel Martin, whom he married in 1943, four children, and seven grandchildren.

News Notes

The **North Carolina Board of Medical Examiners** reminds our members that anyone representing himself or herself as a physician assistant must be approved to perform medical acts by the Board of Medical Examiners of the State of North Carolina. Further, the Board advises that the initials "P.A." stand for "physician assistant" and any individuals who identify themselves in this fashion should be thoroughly familiar with the General Statutes of the State of North Carolina, particularly section 90-18.1.

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Letters to the Editor

Religion and Medicine

To the Editor:

I would first like to applaud the article "Thoughts on the beliefs of religious and medical institutions" by Dr. Albert Warshauer in the January issue of NCMJ (1985;46:29-32). The article presents a brief but thought provoking and thoughtful discussion of a number of practical as well as ethical problems of medical practice today. I would suggest not only practitioners but medical students as well should read and digest this excellent communication.

I am especially concerned with problem number 4 in the article, namely blood transfusion as it applies to the Jehovah's Witness patient. Dr. Warshauer has written a very good summary of my own personal feelings regarding this particular problem. Additionally, his summary in number 9 on medical fees and malpractice awards is a very good summary of the problem.

I disagree however on the role of the physician in regard to some of the social-political areas such as the Vietnam war, civil rights, and more recent problems of drought and areas of famine. Some of these problems are natural, which none of us have control over. Some are political and I do not deny that physicians should have political involvement, but the problem is much larger than we, representing 0.4% of the population of the United States, could hope to accomplish. In regard to promoting the use of seat belts, I think that the medical profession has tried; however, the general population just does not seem to be interested. To use an old cliche, "you can lead a horse to water but you can not make him drink."

By the way, does anyone know of a physician who is a Jehovah's Witness?

Again, my thanks for a very interesting, timely, and thought provoking article.

Lloyd F. Redick, M.D.
Department of Anesthesiology
Duke University Medical Center
Durham 27710

Several physicians responded to the February 1985 Physicians' Forum question about patients who refuse lifesaving treatment, among whom Jehovah's Witnesses may be counted (NCMJ 1985; 46:89-92).

CORRECTIONS

In the article "Common Mononeuropathies" by E. Wayne Massey, M.D., published in the January 1985 issue of the NCMJ, figures 5 and 8 were inadvertently switched. Plates I through VI were reprinted with the permission of the publisher, W. B. Saunders Company, from Haymaker and Woodhall, *Peripheral Nerve Injuries*.

In the article "Interactions Between Digitalis and Antiarrhythmic Drugs" by Thomas L. Wenger, M.D. and Harold C. Strauss, M.D., C.M., published in the January 1985 issue of the NCMJ, figures 1 and 2 were reprinted with permission from Leahey EB Jr, Reiffel JA, Giardina EGV, Bigger JT Jr. The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. A prospective study. Ann Int Med 1980;92:605-8.

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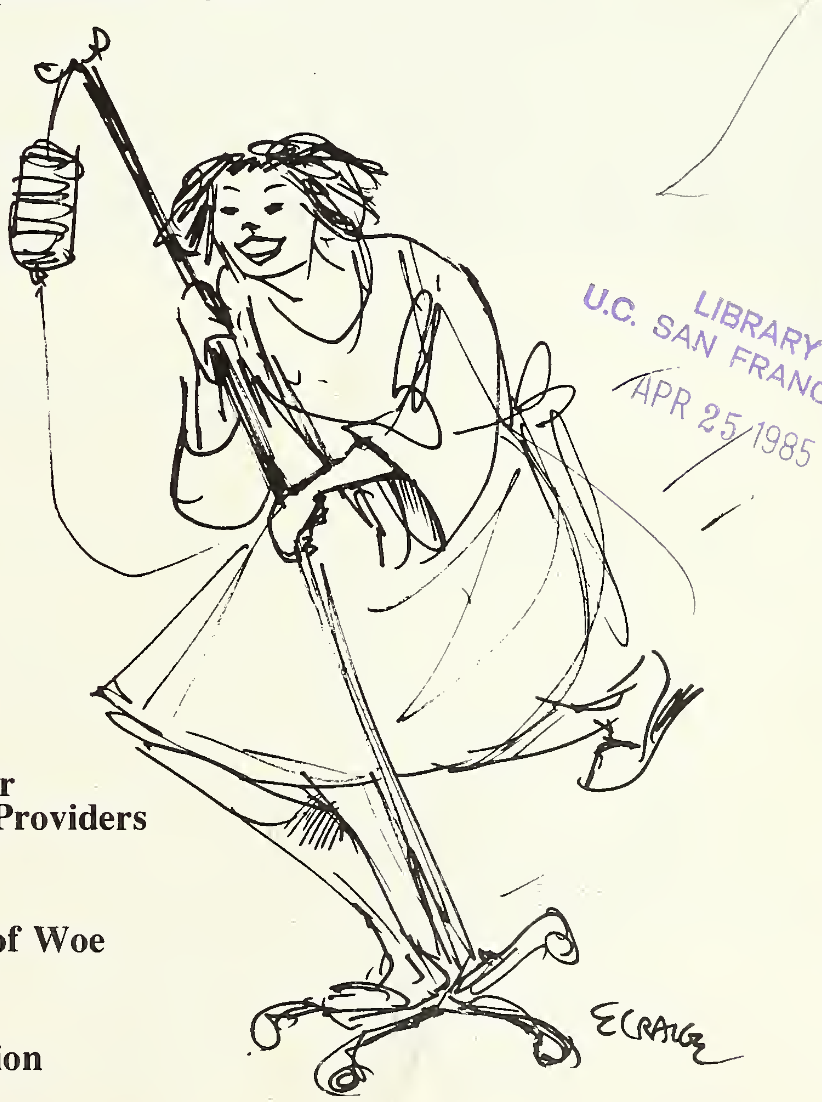
A young woman with a fatal illness and a strong desire to truly live each day until her last causes the staff of a coronary care unit to rethink and, in the end, restructure their treatment of terminal patients. page 197



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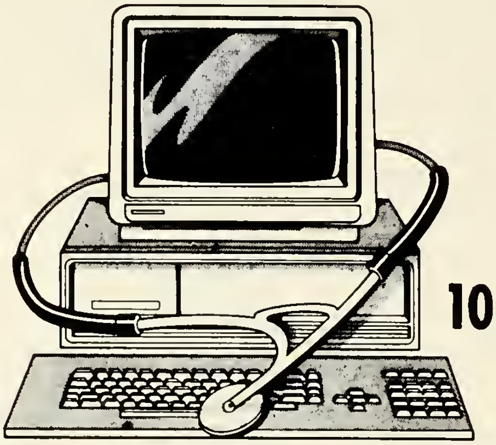

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Sessions of the HOUSE OF DELEGATES will convene in the Cardinal Ballroom, Pinehurst Hotel, Pinehurst, North Carolina, at the following times:

Thursday, May 2, 1985 — 10:00 a.m. — Opening Session
Saturday, May 4, 1985 — 2:00 p.m. — Second Session

A member of the CREDENTIALS COMMITTEE will be present at the Desk in the Hotel Lobby, Wednesday, May 1, 1985, 3:00 p.m. to 5:00 p.m., and Thursday, May 2, 1985, 8:30 a.m. to 10:00 a.m. to certify Delegates. Delegates are urged to bring their Credential Cards for presentation at the Registration Desk. Delegate Badges must be worn to be seated in the HOUSE OF DELEGATES.

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EDITORIAL

Short Term Goals for Young Health Care Providers

Donald D. Neish, M.D.

I'M no wordsmith with the skills of a Lewis Thomas, but the Lives of My Cells may have enough experience for me to qualify as Sage for my son, The Medical Student, my daughter, The Nurse and all of their friends who have chosen to become Health Care Providers. What a crass designation that is!

My loved ones, their friends, and I are stretching ourselves to the limit each day, laboring for the strangers we meet and treat as patients — sorry, clients. These distressed humans, who are sick, don't remain strangers to us very long, because we soon begin to serve them in the finest tradition of caring for The Consumer of Health Care as outlined years ago by Dr. Francis Peabody. (The secret in caring for patients is to care for the patient.)

The Medical Student visits. Not wanting to go through the rigors of medical school again myself, I'm relieved that he drops in only on occasion, his mission a good meal, to do laundry, or to ask the old man how he got through medical school in the Fifties. I allow it may have been easier then, because we did not have to deal with the explosion of knowledge now extant.

Being blasted by the anatomy and biochemistry his first year has not burned out the caring part of him. He cares for the patients that first year med students are allowed to interact with, cares for his classmates, who are stressed more than at any time during the pre-med days. He cares for himself, is amazed how the pressures build up and cause even healthy young bodies to cry out in pain when pushed too hard.

What can I say to him when he hurts? I remember my first year in medical school, the panic, the grinding fatigue, the dragging out of bed in the morning to face another impossible day. Yet, I can see my old self in his eyes and in what he says. He loves the challenge of his chance to acquire new and exciting medical knowledge. He hopes he can put it all to good use some day, at the research bench, or the bedside, because he cares for people.

Regardless of what the for-profit corporate medical plans, the Feds, the lawyers, or an envious public do to us, they will never be able to take our caring away from us. Neither can we be bored for very long, because new things will stimulate us to be students of the human condition for the rest of our professional lives.

So, I convey to him as best I can: 1) You picked it son, and you and your friends will have to learn to cope with it all, each in your own way. 2) I'm confident you will survive, as I did. You have better maturity and skills than I had at your age. 3) You love it. Admit it. That will keep you going during the rough times.

I take a phone call from The Nurse. Like her brother, she chose her profession with my blessing, but not my pressure. After getting her degree, she could have picked some laid-back office job, but no, there she is in the Teaching Hospital, working those shifts that cause the body's biologic clock to protest: cruel and unusual punishment. She cares, and the hospital staff sees that, the patients and families warm to it. Professionalism and caring, that is where she gets her daily worthwhiles.

She and I get to see the house staff Providers and how they are knocked about. All the old intern and resident problems I remember are still there, even though the participants are renamed PGY-1s or some such. There are the frustrations, the sleep deprivation, the highly charged contacts with patient, family, attendings — the daily confrontations with vulgarity and death.

I feel for you, Young Health Care Providers. I was almost a pediatrician myself once; now I do a fair bit of geriatrics, but I feel for those pediatric house officers. In my practice, I have to deal with all those over-the-shoulder-watchers who wish to tell me the best way to handle the last days of terminal aging. I can hardly believe the recent prediction that I may live to see the controversy rise to such a pitch that there will be ''Granny Doe'' legislation to contend with.

In addition to ''Baby Doe,'' the pediatrician faces many new snares and delusions. One of Walt Kelly's POGO characters said, ''We have met the enemy and they is us.'' Is that an explanation for recent events? The delicate interplay involving father, mother, infant and physician is now complicated by the use of a vital organ of a baboon. One wonders how the animal was approached to give its informed consent.

As life gets more complicated for us Providers, I can only fall back on ancient wisdom: Attention all Health Care Providers.

Have short term goals as well as long ones. With love and enthusiasm, you can get through the next hour. If you made a mistake, learn from it and forget it; the next hour demands your undivided attention. You certainly can get through the next day, the next few days. You will make it through anatomy, son, or that last night on duty before your two day break, my daughter. PGY-1, you can survive this rotation.

Ask yourself, people, is there anything more interesting,

From 2609 N. Duke Street, Durham 27704.

more rewarding to you, than medicine? If there is, you had better be out and doing it soon. If not, dig in and enjoy the present. The past can't be undone; the future is uncertain, but for you, because you care, it can be a bright one. Hang tough, The Sage is watching you with love. He still cares too, after these many years in practice, and there is no bureaucracy, no third party that can take that away. Thanks Dr. Peabody, we still remember you.

EDITORIAL

Sometimes It's Tough to Make a Living

John H. Felts, M.D.

ONE of the difficulties in making a living is constant exposure to things at work which can cause a multitude of problems. The names of some of them — housemaid's knee, weaver's bottom — can't be improved upon nor can the ones given to some injuries incurred at leisure — jogger's nipple, tennis elbow. And tennis elbow can strike in the non-swinging arm of those who don't even play tennis, provoked by less athletic maneuvers.

In recent months, the textile industry has been criticized because many of its workers, male and female, develop arthritic difficulties in their wrists and shoulders, thoracic outlet and carpal tunnel syndromes, for example. The industry is accused of all sorts of nefarious deeds because it can't seem to produce a symptom-free, risk-free workplace and is, it sometimes seems, held responsible for its employees' pre-employment anatomical development. There are many textile manufacturers really genuinely concerned who are doing what they can to ease the strain, meanwhile wondering how to cope with imports from the Orient.

There aren't many easy solutions for either problem but the industrial worker may be better off in terms of work hazards and third-party medical coverage than the fast disappearing, much written about, oft idealized small farmer in the United States. Some of our politicians still sound on television, today's synthetic stump (or hustings if you prefer), as if more than 50% of us live in the country, acquire our moral stamina from the soil and can't survive without tobacco, milk or honey price supports from Washington, all the while demanding that government get off our backs. The small farmer, now commuting to town to work during the day at a factory, needs some attention at a practical level, not from remote reformers, because his family is subject to all natural risks imaginable. When there were more farmers, cotton and the boll weevil and tobacco and blue mold made headlines but now carcinogenesis and brown lung threaten. Little wonder farmers continue to go to town for work which isn't as demanding as that on the idyllic family farm reached by muddy roads, threatened by dry wells and blessed by cold privies which certainly contributed to making constipation a major medical problem only yesterday. Cold, even icy, wooden seats and bare bottoms are rarely compatible.

Yet when occupations are changed from country to town or even when we acquire new things, we enter new zones of risk as we escape from the old. Take the Honda hip, as yet unreported in our medical literature. A patient of mine, enticed by Japanese design and the promise of more economical maintenance, traded in his car for a new Honda Civic. His build, however, was such and its left front seat such that they didn't fit and he developed right hip pain and stiffness after driving short distances. Highly touted nonsteroidal anti-inflammatory drugs provided little relief. Cure of his Honda hip was economic but at some financial loss in trading his new Honda for a car his size.

Hands and wrists come in for trauma too. The farmer's wife who gets tobacco-seasonal carpal tunnel syndrome requiring surgery in the winter, for one. And what of the cotton buyer at his work for more than 30 years who was referred before we could measure parathyroid hormone in the blood, because erosions of the medial aspects of his second (middle) phalanges were interpreted radiologically as indicative of hyperparathyroidism? A cotton buyer tests for tensile strength and other characteristics by grasping a sample between the first and second fingers of each hand and pulling it apart. More than 30 years of sampling can cause traumatic erosions of bone. And, finally, the middle-aged lady with recent onset of hand pain and stiffness without a history suggestive of Raynaud's phenomenon or physical or laboratory signs indicative of arthritis. A careful occupational history told the tale. She was a chicken packinghouse worker who supervised a conveyor system transporting carcasses for a last washing before packing. She had been at the job for several years but a few weeks before her symptoms began, a new system, which fed water from above as well as below, had been installed. The water was cold, her hands stayed cold and wet and she had hand angina from vacoconstriction and ischemia induced by the cold. When she was transferred to a dry job, her symptoms disappeared.

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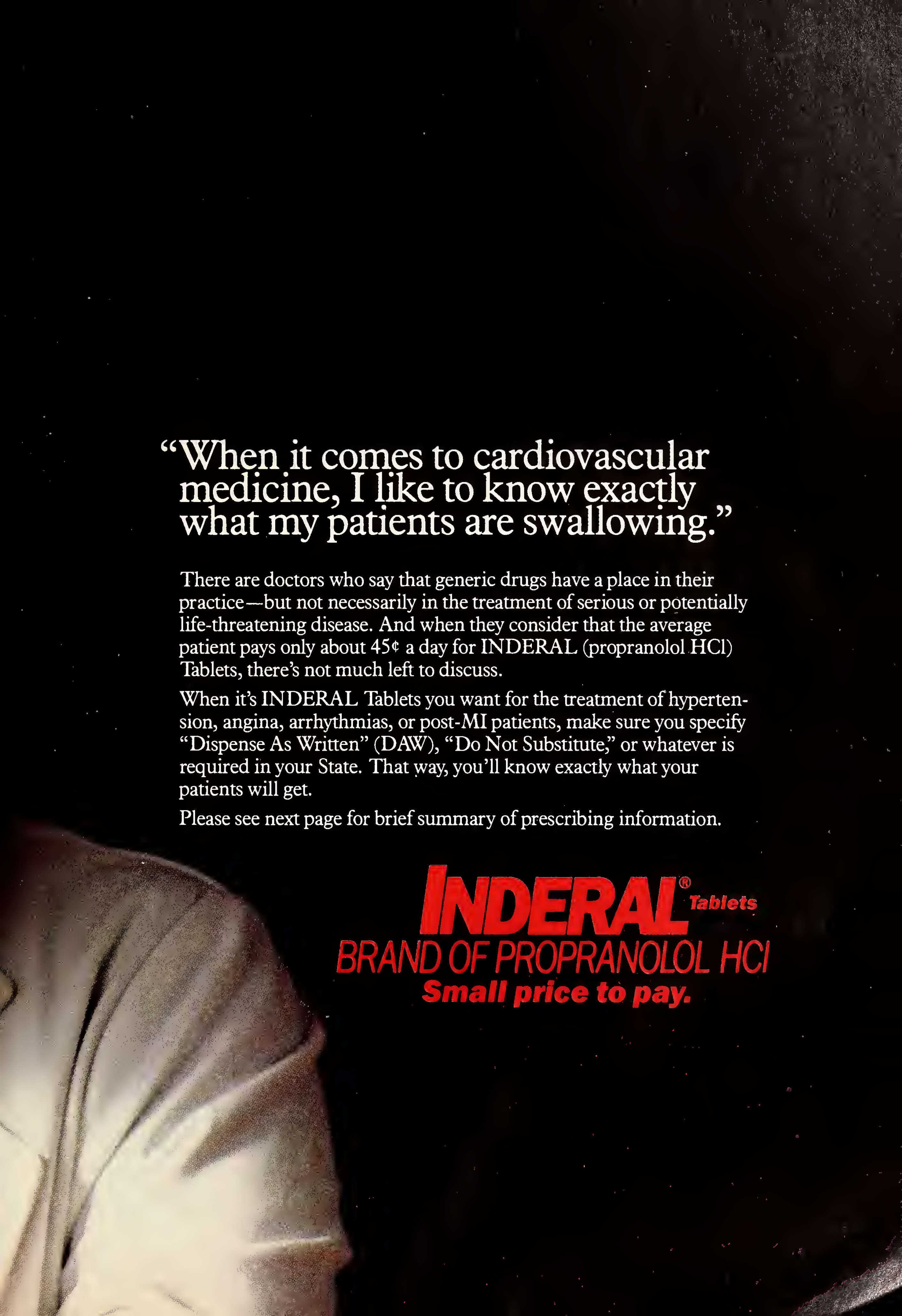

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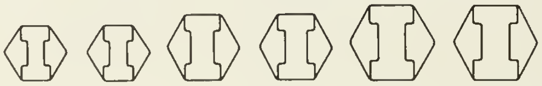

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CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock 2) sinus bradycardia and greater than first degree block 3) bronchial asthma 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS

CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS

General Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers. INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

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SPECIAL ARTICLE

Balloons on the CCU

Charles Shunior, B.S.N.

- *The dying of a vital, vibrant young woman on the CCU brings some changes to the high-tech approach the unit usually employed with its seriously ill patients.*

BALLOONS are a gesture of mirth, connoting youth and playfulness. But when a garland of balloons recently appeared in our coronary care unit, it commemorated not a birthday or a promotion but a death, and a painful, tragic one at that. Yet it occurred to no one to regard the gesture as ghoulish or in poor taste. The donor was a young university instructor whose wife had died exactly one year before in our Coronary Care Unit (CCU).

Before Elaine came to the CCU we rarely questioned our approach to gravely ill patients. The issue seemed basically straightforward: we saw death as the fundamental enemy and any time rescued from its clutches as a victory. The struggle admitted little ambiguity. We were heroes in a John Wayne western; our patients, helpless frontier maidens; death, a savage ravager. If we grudgingly conceded that, for certain patients, ''the time had come,'' it was for some other area of the hospital to direct this inferior script. ''No codes'' were alien to the moral landscape of the CCU. As long as a patient remained in our province our directive seemed clear: wrest minutes or days from the maw of death.

We knew that outside the austere domain of intensive care units a different way of understanding death and dying had been gaining some prominence. Spurred to consciousness by the hospice movement and by writers such as Elisabeth Kubler-Ross, death was seen not merely as an endpoint but as a process which could be accomplished with greater or lesser skill, grace, and reward. One ramification of this perspective was a therapeutic stance oriented not toward an impossible recovery or the staving off of an inevitable death but toward helping the patient to die well.

To us in the CCU the urgings of thanatologists seemed a remote whisper. Reversible emergencies, not chronic terminal illness, were the grist for our mill. Nevertheless, troubling questions lingered behind the backdrop of our familiar routine. What of patients who suffered acute illnesses on top of irreversible disease processes, such as the metastatic cancer patient who has sustained a heart attack? We treated such patients with a split mind. We noted their presumably terminal condition, but allowed them to be swallowed into the high-tech gut of the hospital's ''business-as-usual'' therapy system.

Into the middle of our veiled ambiguity came Elaine, fighting for breath in severe congestive heart failure. A year ago she had been one of our telemetry patients, and we had known her with affection as an attractive young woman whose sense of fun was undampened by a diagnosis of viral cardiomyopathy. Relatively symptom-free during her previous hospitalization, she had kept the staff holding their breath and smiling despite their concern as she sailed down the corridors using her IV pole as a scooter. Her large brown eyes twinkled with vitality as she talked about issues of life and a death that seemed so distant.

She came back to the CCU after a rapid and drastic decompensation, already on a respirator and dependent on intravenous cardiotonic medicines. Within a short while sepsis and renal failure were added to the list of her problems. Elaine's room eventually looked like a high-tech health fair as her bed, already lost in a forest of infusion pumps, became surrounded by a cooling blanket generator, a cardiac output computer, and a panoply of peritoneal dialysis equipment. Somewhere in the middle of all these gadgets was a young woman, scared, hungry to live, whose heart was hopelessly broken. Although, by themselves, her acute emergencies or complications were potentially reversible, even her candidacy for heart transplantation had been ruined by her systemic complications.

With a patient as young and lively as Elaine, the nursing and medical staff are drawn to hope for miracles. We played all our aces, fighting day by day for the miracle to happen. And Elaine fought for it too. A partner in all medical decisions, she struggled to the end for more time, requesting only days before her death that a chest tube be inserted, buying her more hours or days at the cost of more suffering.

Even as we hoped for miracles, the massive reality of death was our ever-present backdrop. No one, from the attending physicians to Elaine herself, had any real illusions about the final outcome of the struggle. During one of Elaine's relatively uncomplicated periods I permitted myself to think that her disease was in remission and that she might yet recover sufficiently to leave the CCU. When I shared this idea with Elaine she smiled and shook her head as a mother might to disillusion a child's over-enthusiastic assessment of the power of Santa Claus.

But if Elaine were not a ''viable'' patient, what was the point of all our efforts and all her pain? If our Faustian struggle against death were doomed to fail, should we not

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From the Coronary Care Unit, North Carolina Memorial Hospital, Chapel Hill 27514.

in that case withdraw her elaborate life supports and let her go in peace? Elaine herself resolved this ethical dilemma by her unrelenting thirst for life, for one more day of struggle. The high-tech gadgetry kept beeping; and the dialysate, the antibiotics, and the cardiotonic drugs kept flowing.

Gradually we sketched in the outlines of a new way to care for terminal patients in an intensive care unit setting. This model affirmed the propriety of advanced medical support for terminal patients such as Elaine. The tradeoffs between comfort and safety were not automatically made in favor of comfort. Swan-Ganz catheters, chest tubes, and dialysis machines were seen to be appropriate aspects of dying, as they were for Elaine. But in the context of all this high-tech life support we endeavored to provide low-tech life enhancement, remembering that death is always in the background of the scenes we enact in the CCU. Elaine helped us learn to focus day by day not on "saving" patients at all costs nor on helping them directly to "prepare for death," but rather on creating a space for the patient in which maximum real living could continue. In answer to the question "Why are we expending so much time, so many resources, and so much emotion to help a dying girl live a few more days?" we could answer that, from the perspective of eternity, all of us have only a few days left and that the goal of the healing arts should not be merely to stave off death but to empower us within those few days to approach the highest possible personal attainment. In order for this answer to be honest we must focus — even in the CCU — not merely on the protection of life but on its enhancement.

So it was that housestaff and nurses found themselves gathered around Elaine's bed serenading her with her favorite folksongs while the medical resident joined her husband in a guitar duet. And so it was that nurses and the respiratory department solved the complicated problems of transporting an intubated patient from the CCU to an outdoor patio in order to reunite Elaine with her somewhat bewildered but faithful dog. And that members of Elaine's family were present at her bedside around the clock; sometimes merely being with her; sometimes browsing through old photo albums, affirming the goodness, the fullness of her life. During those times when Elaine was not intubated, her mother would share with her the hardest words, making funeral plans and talking about life after death.

A member of the Department of Psychiatry who had known Elaine before her hospitalization came frequently to the CCU during the last weeks in order to coach her in meditation techniques for stress reduction.

A journal was kept at Elaine's bedside, and visitors to her room, whether staff or family, were encouraged to write their observations, reflections, and suggestions. We originally thought that the book would improve professional communication among the many persons who shared Elaine's care, but it soon became evident that writing in the journal provided the staff with a record of our own growth as nurses, doctors, and human beings.

One morning Elaine's heart rate began to slow down and its rhythm deteriorated. I whispered to her that the time was drawing near, that I knew she was ready. Using a theme we had explored for meditation purposes, I reminded her that if she softened herself, gave up resistance, the wave would take her gently, as a mother carries a child to bed. She closed her eyes, took her husband's hand, and died.

The memorial service held the next week for Elaine employed the Quaker format of allowing persons to spontaneously "witness" their love and grief. Physicians, nurses, technicians, personal friends and family all spoke. Passages from the bedside journal were read and we all joined in singing songs she had loved. Besides being a memorial to Elaine, this service commemorated acceptance by the hospital community of our new way of caring for dying patients in ICUs. Near the heart of our grief was the satisfying knowledge that our unit had found an identity as a healing environment for the terminally ill ICU patient.

In the months following Elaine's death we have tried to strengthen this healing environment. The unit has been redecorated to look less forbidding, more homelike. Noise control is emphasized, and visitation policies are custom-tailored to the emotional and physical needs of the patients. Staff are routinely oriented to techniques of stress reduction and emotional counseling. Periodic group discussions on issues of death and dying help us to clarify our own responses to guiding patients through the valley of the shadow.

Above all Elaine, and the balloons that came in her memory, remind us to bring to our patients songs as well as medicines. Life — with its fantastic range of physical and emotional cravings, its need not just for bread, but for roses — is as miraculous in its last hours as its first.

SCIENTIFIC ARTICLE

When Crohn's Disease Is Not Crohn's Disease

David A. Forsberg, Thomas C. Wall, M.D., John T. Garbutt, Jr., M.D.

- *The key to Crohn's disease is chronicity.*

THE diagnosis of inflammatory bowel disease carries serious long-term implications. Both Crohn's disease (regional enteritis) and non-specific ulcerative colitis are considered illnesses with poor prognoses. When the physician makes this diagnosis he must understand that he is possibly committing the patient to (1) long-term medication, (2) decreased insurability (health and life insurance are difficult to obtain and more costly), (3) difficulty in securing employment and (4) severe psychosocial stress as the patient becomes familiar with the expected course of his disease.

The following case report illustrates the danger of premature diagnosis.

Case Report

A previously healthy 22-year-old white male medical student presented to the Emergency Room with a history of abdominal pain, malaise, lightheadedness and low grade fever of 48 hours' duration. He denied nausea, vomiting, or change in bowel habit. On physical exam vital signs were normal, temperature was 37°C and right lower quadrant pain maximal at McBurney's point with mild rebound tenderness was present. Rectal exam was normal except for a tender right gutter, and stool was guaiac negative. Pertinent lab values included WBC 8100 with a normal differential. A flat plate of the abdomen revealed possible calcification in the right lower quadrant consistent with an appendolith.

A tentative diagnosis of appendicitis was made and the patient underwent surgical exploration. Operative findings included a normal appendix and an 8 cm length of thickened, inflamed terminal ileum. Intraoperative cultures for routine pathogens were negative. A diagnosis of terminal ileitis, probably Crohn's disease, was made. Simple appendectomy was performed without bowel resection. The patient was started on a prednisone taper and later sulfasalazine (Azulfidine) therapy. The patient and his family were informed of the existing diagnosis of regional enteritis. It was recalled that a distant cousin had Crohn's disease.

Since the patient was a medical student he had some knowledge of inflammatory bowel disease and its sequelae. His further reading on the subject was clearly depressing. Further emotional stress ensued when he was informed that he might have to consider changing his career goals in surgery as a result of the unpredictable and serious implications of this illness.

However, the postoperative course was complicated by the onset of profuse bloody diarrhea on the fourth day. There was no history of foreign travel, seafood ingestion, animal exposure, antibiotic exposure, or homosexual experience. Proctoscopy at that time revealed diffuse friable granularity, no discrete ulcers and a purulent stool on microscopic smear. Cultures for enteric pathogens were positive for Campylobacter fetus jejuni. Although subsequent x-ray revealed changes felt to be typical of Crohn's disease in the ileum and cecum (figure 1, left), the clinical diagnosis was now felt to be bacterial dysentery due to Campylobacter.[1-5] Prednisone and sulfasalazine were discontinued and the patient was treated with a 7 day course of erythromycin 500 mg po q.i.d. with complete resolution of all symptoms. He has remained well for an 18-month follow up and repeat UGI with ileal x-ray is now normal (figure 1, right).

Table 1
Differential Diagnosis of Dysentery

- **Specific Infections**
  - Campylobacter
  - Shigella
  - Salmonella
  - Yersinia
  - Gonorrhea
  - Tuberculosis
  - Lymphogranuloma venereum
  - Non-LGU Chlamydia
  - Amebiasis
  - Schistosomiasis
  - Syphilis
  - Fungal infections (e.g., Histoplasmosis)
  - Vibrio enterocolytica
  - Viral etiologies
  - Pseudomembranous colitis
- **Non-Specific Inflammatory Bowel Disease**
  - Ulcerative colitis
  - Crohn's disease
- **Mechanical Factors**
  - Radiation colitis
  - Chemical proctitis
  - Ischemic colitis
- **Systemic Diseases**
  - Amyloidosis
  - Systemic lupus erythematosus
  - Hemolytic-uremic syndrome
  - Scleroderma
  - Vasculitis
  - Behcet's syndrome
  - Neoplasia (lymphoma, leukemia)

From the Division of Gastroenterology, Department of Medicine, Duke University Medical Center, Durham 27710.

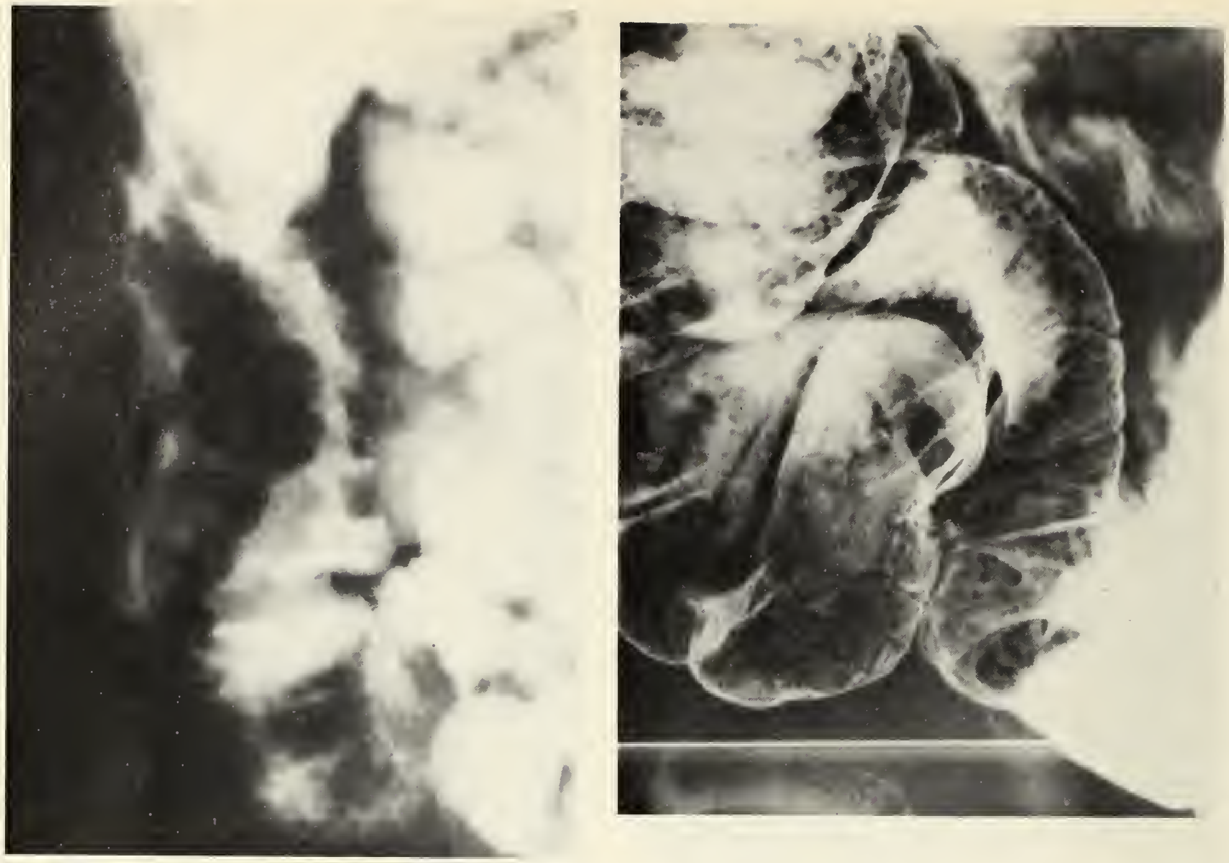

Figure 1. *Left: Severe inflammation of distal ileum and cecum. Right: Complete resolution of inflammation after antibiotic treatment.*

This case illustrates that a diagnosis of regional enteritis or ulcerative colitis generally should not be made at the time of first symptoms. Rather the diagnosis of inflammatory bowel disease (ulcerative colitis, regional enteritis) should imply chronicity and recurrences and is a diagnosis of exclusion. Many infectious etiologies may produce ileitis or colitis mimicking inflammatory bowel disease.[6, 7] These include Campylobacter, Shigella, Salmonella, and Gonococcal infection in the U.S., as well as amoeba and tuberculosis if foreign travel has occurred. Appropriate cultures are the key to correct diagnosis. While uncommon, such an acute infection may mimic a surgical abdomen, necessitating laparotomy.[8, 9] At such a time, appropriate cultures should be obtained. Mechanical factors such as radiation or ischemia must also be considered but the history is usually self-evident. Pseudomembranous colitis due to prior antibiotics usually has a classic endoscopic appearance. A variety of systemic illnesses may also have gastrointestinal manifestations and must be included in the differential diagnosis. Table 1 presents a partial list of the diseases which should always be considered before making the diagnosis of inflammatory bowel disease.

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SCIENTIFIC ARTICLE

Familial Thrombotic Disorders

John J. Stuart, Ph.D., M.D. and M. Robert Cooper, M.D.

- *Two brothers with recurrent thrombosis and phlebitis in their legs have low levels of protein S, a recently discovered natural anticoagulant.*

IN the past thirty years our knowledge of the blood clotting system has advanced from crude experiments employing nothing more complicated than test tubes to complex enzymology yielding almost overwhelming detail about molecular structure and kinetics. These advances have greatly improved the diagnosis and treatment of bleeding disorders so that it is now rare to find one the cause of which is undiagnosable. Such is not the case, unfortunately, with thrombotic disorders. Despite a wealth of information about the natural anticoagulants existing in the plasma and endothelial cells, the cause of venous thrombosis in many patients remains obscure and the treatment non-specific.

Recently the discovery of two new naturally occurring anticoagulants, proteins C and S, has explained the cause of two rare familial thrombotic tendencies.[1, 2] This report describes the clinical course of protein S deficiency in two brothers and will attempt to review in a practical fashion the subject of familial thrombotic disorders.

Case Report

The patient first developed deep venous thrombosis of the right leg at age fourteen after a fall. Despite treatment with warfarin, deep venous thrombosis recurred requiring hospitalization for treatment with heparin. At age sixteen, he developed a severe rash from warfarin and was changed to subcutaneous heparin on an outpatient basis. Laboratory evaluation at this time revealed the following tests to be normal: prothrombin time, partial thromboplastin time, thrombin clotting time, fibrinogen electrophoresis and antithrombin three level by immunologic assay. Heparin therapy did not prevent recurrent lower extremity thrombophlebitis which was, however, controlled when he was placed on the long-acting vitamin K antagonist Diphenadione. Control of his disease continued for six years punctuated by recurrent episodes of hemorrhage due to excessively prolonged prothrombin times. This problem prompted discontinuance of his anticoagulation at age 23 but recurrent deep venous thrombosis followed within a month. Diphenadione was restarted but was stopped six months later because the drug was withdrawn from the market. Since that time his phlebitic tendency has been reasonably well controlled by 10,000 units of heparin self-administered twice daily, but superficial thrombophlebitis of the legs, abdomen and chest occurs sporadically. Post-phlebitic syndrome with recurrent malleolar stasis ulcers has been a major source of disability.

The propositus has three siblings. A younger brother developed recurrent lower extremity phlebitis at age fifteen, also after mild trauma, and has been on warfarin since that time. A sister and another younger brother have no symptoms, nor do the parents. The only other family member with phlebitis is the paternal grandmother who developed it at age 58 after undergoing hip surgery. Table 1 shows the protein S levels in this family as determined by Dr. Philip Comp.[3] Presumably, the brothers are homozygous for protein S deficiency while their asymptomatic parents are heterozygotes. The phlebitis in the grandmother with a normal protein S level can be related to antecedent surgery.

Protein C and Protein S Deficiency

Deficiencies of protein C and protein S are similar clinically, presenting as recurrent deep and superficial venous thrombosis. These two naturally occurring anticoagulants are similar also in being dependent on vitamin K for their synthesis as are the procoagulant clotting factors II, VII, IX, X. The activation of protein C probably occurs simultaneously with the laying down of fibrin clot at an injury since protein C, like fibrinogen, is activated by thrombin.[4] In the case of protein C, the thrombin must be bound to a protein, thrombomodulin, which in turn is bound to endothelial cells, in order that activation take place. Activated protein C is capable of destroying activated factors V and VIII proteolytically and therefore damping clot formation. The thrombomodulin-protein C pathway exerts, therefore, negative feedback inhibition on clot formation.

Protein S appears to function as a cofactor for activated

Table 1

Individual	Age	Symptomatic	Protein S Level (%)
Propositus	29	Yes	<5
Brother	18	Yes	<5
Brother	16	No	80
Sister	25	No	85
Father	48	No	15
Mother	47	No	30
Paternal grandmother	73	Yes	101

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Table 2
Familial Thrombotic Disorders

Disorder	Diagnostic Test	Availability of Test
Antithrombin III deficiency	Immunologic and functional assay	Widely available
Protein C deficiency	Immunologic and functional assay	Research lab only
Protein S deficiency	Immunologic and functional assay	Research lab only
Plasminogen deficiency	Immunologic and functional assay	Some commercial labs
Plasminogen activation deficiency	Functional assay	Research lab only
Fibrinolytic inhibitors	Functional assay	Research lab only
Dysfibrinogenemia	Thrombin clotting time	Widely available
	Kinetic analysis	Research lab only

protein C.[5] By binding to protein C, it greatly increases the rate at which activated protein C is able to destroy activated factor V.

The Naturally Occurring Anticoagulant System

Prior to the discovery of protein C and protein S, the naturally occurring anticoagulants in the fibrin-forming system (the interacting platelet system will not be discussed) were limited to plasminogen and antithrombin III (heparin cofactor). In addition, some molecular variants of the fibrinogen molecule were known to result in a thrombotic tendency. Each of these proteins will be briefly discussed.

Plasminogen

The concentration of plasminogen in human plasma is about 21 mg/100 cc. During tissue injury plasminogen, activated by enzymes released from the injured endothelium, becomes the active serum protease plasmin. Because plasminogen has a high binding affinity for fibrin clot, under physiologic conditions plasmin is generated in proximity to the protein (fibrin polymer) that it is meant to destroy. Any plasmin generated in the blood stream in the vicinity of the clot is neutralized by inhibitor proteins of which the most important is the alpha-2-plasmin inhibitor. Thereby non-specific action of plasmin on circulating fibrinogen and coagulation factors such as V and VIII is prevented. In the pathologic state of disseminated intravascular coagulation, so much plasmin is generated that the inhibitor system is overcome and large amounts of fibrin(ogen) degradation products are generated.

As might be expected, mutation resulting in amino acid substitutions in plasminogen can result in a less active enzyme and an inherited tendency to deep venous thrombosis. In the cases reported so far, the immunologically measurable plasminogen has been normal but the mutant enzyme has had decreased functional activity.[6, 7] Deficiencies of endothelial plasminogen activation[8] and naturally occurring inhibitors of fibrinolysis[9] have also been reported to result in thrombotic disease.

Antithrombin III Deficiency

The plasma protein antithrombin III (AT-III) is the most important inhibitor of thrombin. A partial deficiency of AT-III causes recurrent deep venous thrombosis. The homozygous condition with zero AT-III levels has not been observed and is probably incompatible with life. The anticoagulant action of heparin is mediated through AT-III. The non-covalent AT-III-heparin complex has a greatly increased affinity for thrombin and other activated procoagulant factors when compared with AT-III alone. The prevalence of AT-III deficiency has been estimated at one per 2000.[10] The inheritance pattern is autosomal dominant with variable penetrance. Usually the antigenic level of AT-III is decreased but occasional families have a pattern of functionally deficient AT-III which is present in normal quantities when measured with standard immunologic techniques.[11]

Dysfibrinogenemia

The process by which the soluble plasma protein fibrinogen becomes a stabilized fibrin clot through the action of thrombin and factor XIII is complex and leaves much room for errors of nature. More than seventy molecular variants of the fibrinogen molecule have been discovered, most of which are inherited in an autosomal dominant fashion and result either in a bleeding or in a clotting diathesis,[12] but may be asymptomatic. Paradoxically, in some families both bleeding and clotting tendencies coexist. Occasionally the thrombotic tendency affects arteries as well as veins. The concentration of fibrinogen measured by standard immunologic or clotting methods is usually normal. The abnormality is generally easily recognizable, however, because it almost always results in a prolonged thrombin clotting time (TCT). Confirmation of the diagnosis would result from ruling out any other cause of a prolonged TCT or better, from kinetic studies of fibrin monomer formation, polymerization and crosslinking. Treatment of the disorder by anticoagulants is usually successful.

Summary

Opportunities are vast for the occurrence of mutations adversely affecting the function of the many components of the naturally occurring anticoagulant system. A family history of recurrent thrombophlebitis and thrombophlebitis difficult to control with warfarin and heparin are clues that a familial disorder may be present. The lack of other affected family members does not rule out the diagnosis, however, since one may be dealing with a new mutation or with variable penetrance of the disorder. Generally, life-long anticoagulation with warfarin is the treatment of choice.

Table 2 shows the most common familial thrombotic diseases and the diagnostic tests available. There is no doubt that presently unclassifiable disorders exist, the cause of which will eventually become clear as our understanding of hemostasis increases.

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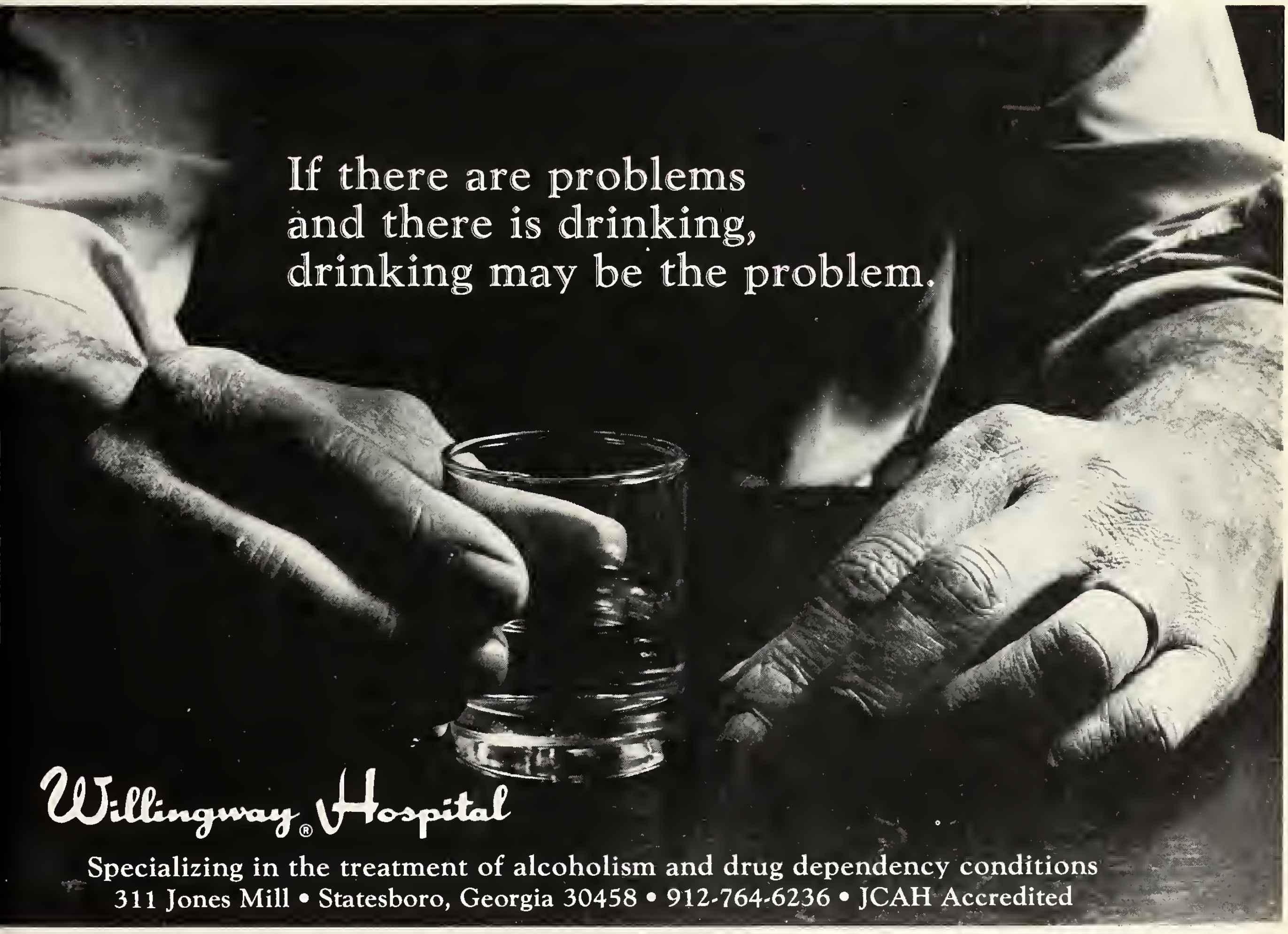

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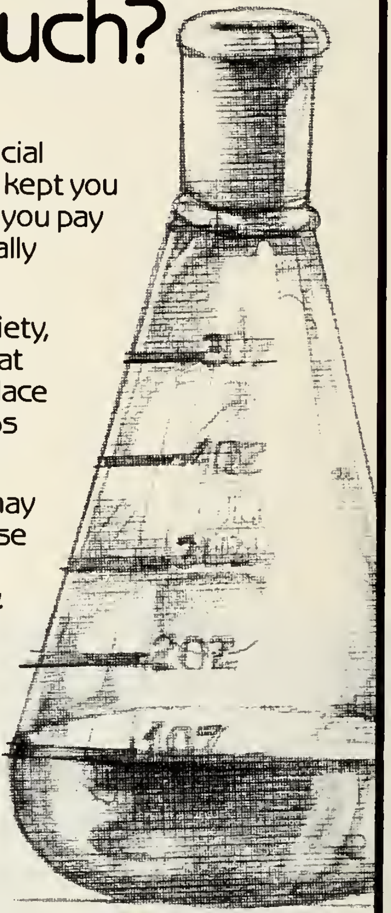

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BALANCED CALCIUM CHANNEL BLOCKADE!

CARDIZEM®
(diltiazem HCl)
balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

2/84

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

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1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
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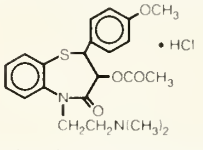
PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3% asthenia (1.2%), AV block (1.1%). In addition, the following even were reported infrequently (less than 1%) with the order of present tion corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradyca dia, palpitations, congestive heart failur syncope.
Nervous System:	Paresthesia, nervousness, somnolenc tremor, insomnia, hallucinations, and amnesi
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomitin mild elevations of alkaline phosphatase, SGO SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivit
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes (vasospastic angina developed periods of transient asymptomat asystole approximately five hours after receiving a single 60-m dose of CARDIZEM.

The following postmarketing events have been reported infre quently in patients receiving CARDIZEM: erythema multiforme; le kopenia; and extreme elevations of alkaline phosphatase, SGO SGPT, LDH, and CPK. However, a definitive cause and effect betwee these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limite Single oral doses of 300 mg of CARDIZEM have been well tolerate by healthy volunteers. In the event of overdosage or exaggerate response, appropriate supportive measures should be employed i addition to gastric lavage. The following measures may be considere

Bradycardia	Administer atropine (0.60 to 1.0 mg). If ther is no response to vagal blockade, administe isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high degree AV block should be treated with ca diac pacing.
Cardiac Failure	Administer inotropic agents (isoprotereno dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarteren bitartrate).

Actual treatment and dosage should depend on the severity of th clinical situation and the judgment and experience of the treatin physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/k and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s i these species were 60 and 38 mg/kg, respectively. The oral LD_{50} i dogs is considered to be in excess of 50 mg/kg, while lethality wa seen in monkeys at 360 mg/kg. The toxic dose in man is not known but blood levels in excess of 800 ng/ml have not been associate with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient' needs. Starting with 30 mg four times daily, before meals and a bedtime, dosage should be increased gradually (given in divide doses three or four times daily) at one- to two-day intervals unti optimum response is obtained. Although individual patients ma respond to any dosage level, the average optimum dosage rang appears to be 180 to 240 mg/day. There are no available data concern ing dosage requirements in patients with impaired renal or hepati function. If the drug must be used in such patients, titration should b carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acut anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safel coadministered with short- and long-acting nitrates, but ther have been no controlled studies to evaluate the antiangina effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (ND 0088-1771-47) and in Unit Dose Identification Paks of 100 (ND 0088-1771-49). Each green tablet is engraved with MARION on on side and 1771 engraved on the other. CARDIZEM 60-mg score tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Uni Dose Identification Paks of 100 (NDC 0088-1772-49). Each yello tablet is engraved with MARION on one side and 1772 on the othe

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SCIENTIFIC ARTICLE

Screening for Congenital Hypothyroidism in North Carolina — 1979-1984

Robert P. Schwartz, M.D.

- *The cost of diagnosing one case of congenital hypothyroidism in North Carolina is $9,618. The cost of institutionalizing one person for 30 years in North Carolina is $1,215,450. The savings afforded by screening are obvious.*

CONGENITAL hypothyroidism is associated with a high incidence of mental retardation. Before screening programs, congenital hypothyroidism accounted for 1-2% of admissions to institutions for the mentally retarded. Only 10% of infants with this disorder attained an IQ of greater than 90 if treatment was delayed over 6 months. The cause of delayed diagnosis is the nonspecificity of signs and symptoms of congenital hypothyroidism which include prolonged gestational age, large posterior fontanel, constipation, jaundice, feeding problems, umbilical hernia, hypothermia, lethargy, and hypotonia. An enlarged tongue is often not present in the newborn period.[1]

In 1972, Klein et al reported that 78% of infants whose congenital hypothyroidism was treated before 3 months of age had an IQ of greater than 85.[2] In 1973, pilot programs for hypothyroid screening were started in Quebec and Pittsburgh. Between 1976-1981, 717,123 infants were screened for hypothyroidism in Massachusetts. One hundred forty-six infants were detected with congenital hypothyroidism for an incidence of 1:4600 live births. Ninety-five of these infants had thyroid scans. Forty-three percent had ectopic thyroid tissue, 22% goitrous hypothyroidism, and 35% had hypoplastic or aplastic glands. In only 4% of these infants was the diagnosis suspected clinically.[3]

In January 1979, a program for hypothyroid screening began in North Carolina. Through the efforts of the Department of Human Resources, the North Carolina Pediatric Society, and the leadership of Representative Patricia Hunt and Senator Ollie Harris, a bill (House Bill 372) to provide funding for hypothyroid screening was passed in the North Carolina legislature. The bill provided $120,000 a year to establish a statewide newborn screening program for congenital hypothyroidism. Between 1979-1982, screening tests were performed by the state laboratory in Raleigh and Dr. George Summer's laboratory in Chapel Hill. Since 1982, almost all tests have been performed by the state laboratory.

Protocol for Thyroid Screening

Blood samples for screening for hypothyroidism and phenylketonuria are obtained by heelstick on all infants prior to discharge from the nursery, regardless of age or feeding status. Infants discharged before 24 hours of age should have the tests repeated by 2 weeks of age. Premature or ill infants, or infants on parenteral feedings should have the tests performed by 7 days of age.

The protocol for hypothyroid screening is to first obtain a filter paper T4 (figure 1). If the T4 is low, an additional T4 and a TSH are performed on the same filter paper specimen. If the repeat filter paper T4 is low with an elevated TSH, the physician is notified by the state laboratory and a STAT serum T4, T3 resin uptake, and TSH are obtained. Infants with a low serum T4 and elevated TSH should have a bone age x-ray (PA of the knee and oblique of the foot) and a technetium thyroid scan. The bone age x-ray may indicate the degree of prenatal insult to skeletal maturation. Most term infants will have distal femoral, proximal tibial and cuboid epiphyses present at birth. The thyroid scan is done for genetic counseling. Infants with a normal sized or enlarged gland on thyroid scan may have a defect in the synthesis of thyroxine. This can be a familial disorder with autosomal recessive inheritance. Absent, ectopic, or dysgenetic thyroid glands can also be identified by thyroid scanning. These are usually not inherited disorders.

Many infants are observed to have a low filter paper T4 and normal TSH. Causes of this condition include prematurity, a deficiency of thyroid-binding globulin (TBG), hypopituitarism, and the so-called euthyroid sick syndrome. When the combination of low T4 and normal TSH is observed, a repeat filter paper T4 and TSH should be obtained. In premature infants, if the repeat T4 is low and the TSH is again normal, it is not necessary to perform any further studies since the low values are due to a delay in maturation of the hypothalamic-pituitary-thyroid axis. In a term infant with a low T4 and normal TSH, serum may be obtained for a T4, T3 resin uptake (an indirect measure of TBG binding sites not occupied by thyroxine), and TSH. A low T4 with an elevated T3 resin uptake is diagnostic of TBG deficiency. A direct measurement of TBG by radioimmunoassay will confirm the diagnosis. Infants with TBG deficiency are euthyroid and require no treatment. Hypopituitarism can also be associated with a low T4 and a normal or low TSH. Extensive evaluation for hypopituita-

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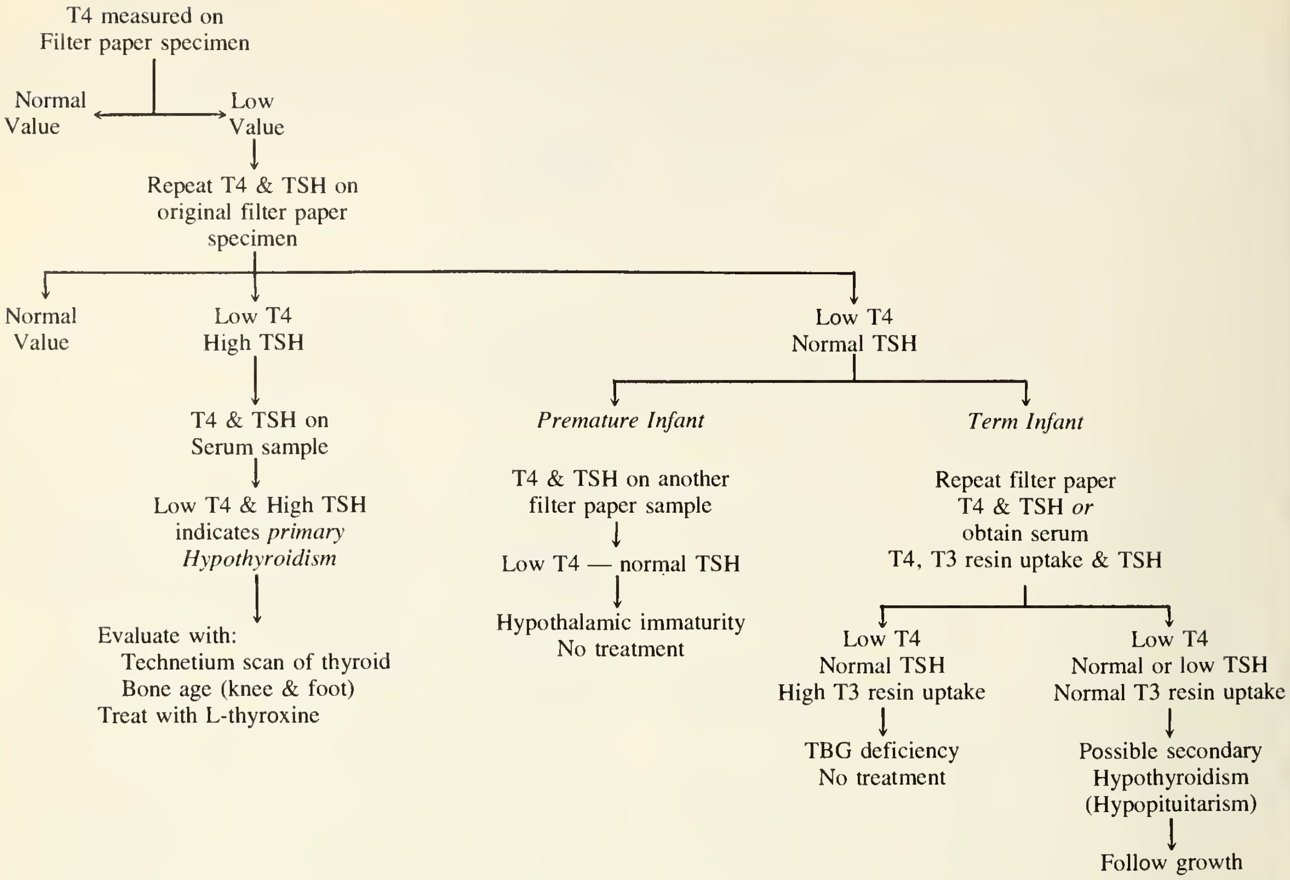
From the Department of Pediatrics, Charlotte Memorial Hospital & Medical Center, Charlotte 28232.

Figure 1. *Protocol for Hypothyroid Screening*


T4 measured on Filter paper specimen
Normal Value
Low Value
Repeat T4 & TSH on original filter paper specimen
Normal Value
Low T4 High TSH
Low T4 Normal TSH
T4 & TSH on Serum sample
Low T4 & High TSH indicates *primary Hypothyroidism*
Evaluate with: Technetium scan of thyroid Bone age (knee & foot) Treat with L-thyroxine
Premature Infant
T4 & TSH on another filter paper sample
Low T4 — normal TSH
Hypothalamic immaturity No treatment
Term Infant
Repeat filter paper T4 & TSH *or* obtain serum T4, T3 resin uptake & TSH
Low T4 Normal TSH High T3 resin uptake
TBG deficiency No treatment
Low T4 Normal or low TSH Normal T3 resin uptake
Possible secondary Hypothyroidism (Hypopituitarism)
Follow growth

rism is not indicated unless there are other symptoms or signs such as hypoglycemia or poor growth. The hypothyroidism which sometimes accompanies hypopituitarism has not been observed to cause mental retardation.

Infants with congenital hypothyroidism are started on treatment with Levothyroxine at a dose of 10 μg/kg/day (0.025-0.05 mg). Thyroid function tests are repeated in 2-4 weeks and are then done every 3 months for the first year and every 4 months the second year. The treatment goal is to keep the serum T4 in the mid to upper range of normal for the age of the infant (8-12 μg/dl). It may take several months for the TSH to fall into the normal range.[4] Linear growth is also an excellent parameter of adequacy of thyroid hormone replacement, and should be followed closely.

Thyroid Screening in North Carolina

Between January 1979 and April 1984, 408,259 North Carolina infants were screened for hypothyroidism. Fifty-eight infants were found to have congenital hypothyroidism, an incidence of 1:7039 (table 1). The decreased incidence of congenital hypothyroidism in North Carolina compared with Massachusetts (1:4600) is related to racial population differences. In Massachusetts, 6-7% of infants are black. Thirty-one percent of North Carolina births in 1983 were black. Only two of the 58 North Carolina cases of congenital hypothyroidism occurred in black infants. In Georgia, the incidence of congenital hypothyroidism is 1:7700. Thirty-seven percent of births in Georgia are black. The incidence of congenital hypothyroidism in Georgia was 1:5526 white infants, and 1:32,377 in blacks.[5]

Fifteen of the North Carolina cases have been seen in Charlotte (table 2). Eight were female and seven male. Fourteen of these infants had technetium thyroid scans; six were found to be athyrotic, five had lingual or sublingual glands, and three had goitrous hypothyroidism. Thyroid scan data are not available for the other North Carolina cases. The average age of treatment for the Charlotte cases was 29.8 days and for all North Carolina cases was 31.7 days (8-231 days). Besides the one infant with a delayed diagnosis at 231 days, another was detected at 82 days and nine at 45-70 days. All other infants were treated at less than 35 days of age. One case was missed by a technician recording error, but was fortunately diagnosed by a physician at 6 weeks of age. Another infant with a goiter was detected at 4 days of age before the screening test result was

Table 1
Thyroid Screening — North Carolina 1/79-4/84

Number screened	408,259	
Normal	395,124	(96.8%)
Insufficient sample	9,272	(2.3%)
Borderline value (41% premature infants)	13,077	(3.2%)
Primary hypothyroidism	58	(1:7039)

Table 2
Charlotte Cases of Congenital Hypothyroidism Detected by Screening Program

Patient	Birth weight (grams)	Sex	Age of treatment (days)	Thyroid scan	T4* µg/dl	TSH† µU/ml	Bone age
1	3773	F	16	Athyrotic	<1.0	>200	Delayed
2	2841	M	17	Athyrotic	1.7	230	Delayed
3	3295	M	47	—	7.4	65	—
4	4204	F	45	Goitrous	4.4	>100	—
5	4318	F	29	Lingual	7.5	59	Normal
6	3909	M	82	Goitrous	8.0	70	Normal
7	4318	F	11	Sublingual	<1.0	560	Delayed
8	3580	M	28	Sublingual	8.2	87	Delayed
9	3382	F	22	Lingual	6.3	279	Normal
10	3773	M	15	Lingual	7.0	>400	Delayed
11	3545	F	21	Athyrotic	<1.0	490	Delayed
12‡	2941	M	4	Goitrous	3.7	>500	Normal
13	3295	F	31	Athyrotic	<1.0	>60	Delayed
14	3664	F	26	Athyrotic	2.5	170	Delayed
15	4290	M	27	Athyrotic	2.3	>100	—

* Normal T4 for first week — 8-24 µg/dl, 1-12 months — 6-15 µg/dl.
† Normal TSH for first week — <20 µU/ml; normal TSH>one week — <10 µU/ml, borderline — 20-60 µU/ml, hypothyroid — >60 µU/ml.
‡ Detected by physician before screening result available.

available. Causes of delay in treatment included insufficient specimens, incorrectly filled out forms, a delay in mailing specimens to the state laboratory, administrative laboratory problems including a shortage of personnel, and delays in getting repeat specimens or a serum specimen.

Cost Effectiveness of Thyroid Screening

Hypothyroid screening has been shown to be cost effective. The cost to diagnose one case of congenital hypothyroidism in North Carolina is $9,618. The cost of institutionalization for 1 year in North Carolina is $40,515. If only 40% of the 58 cases in North Carolina had required institutionalization for 30 years (58 × 0.4 × $40,515 × 30 years), the benefit cost ratio would be 50:1. This ratio would be more impressive were the lost income of untreated or late treated patients taken into account.

Developmental Follow-up

Data on the development of North Carolina infants treated for congenital hypothyroidism are not available. In the New England screening program, however, 146 infants with hypothyroidism had IQs at 3-5 years of age that were similar to controls (siblings or patients with TBG deficiency). These infants were treated at a mean age of 24 days. Patients who had thyroid tissue on scan had higher T4 and lower TSH levels, and less retarded bone age than athyrotic patients. However, there was no difference in IQ in the two groups. The only factor affecting IQ was the adequacy of treatment.[3]

Funding is not yet available for developmental testing of hypothyroid infants detected by screening in North Carolina. It is hoped that an appropriation for this will be forthcoming, so that results in North Carolina can be compared with other programs.

Acknowledgment

The author would like to thank Elizabeth Moore of the Department of Human Resources for providing statistical information, Dr. Louis Underwood at the University of North Carolina for reviewing the manuscript, and Sheila Struewing for secretarial assistance.

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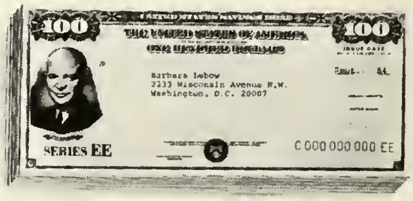

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SCIENTIFIC ARTICLE

Coccydynia: A Tail of Woe

Linda M. Frazier, M.D.

- *What should the doctor suspect in patients with a painful tailbone?*

PAIN in the coccyx is a common symptom, known as coccydynia or "coccygodynia" since 1859 when Simpson, the famous Edinburgh obstetrician, coined the term. From Simpson's specialty one can correctly guess that the condition is more common in women than in men. The following cases illustrate the spectrum of cause, course and treatment of this condition.

Case 1

Four years ago a 39-year-old woman fell, hitting her coccyx on the edge of a landscaping beam. The severe pain subsided after several weeks but intermittent pain, exacerbated by sitting or prolonged standing, remained. She had a habit of sitting with her feet propped on a stool because she was short statured. She had a history of poorly defined anxiety and depression. Two years ago she presented with an exacerbation of coccygeal pain. There was marked tenderness on palpation of the coccyx; pelvic and rectal examinations were normal. Coccyx x-rays showed no fracture (figure 1) and a sonogram of her pelvis showed no mass. A diagnosis of coccydynia was made. She was advised to sit on a doughnut pillow and to use a shorter chair; during two years of follow-up the symptoms have waxed and waned, but no serious coccyx pathology has developed.

Comment: Coccydynia occurs almost exclusively in women: in Hodge's series, 51 of 55 patients were women. Duncan found that 97% of 262 patients with coccydynia were women.[1, 2] The female preponderance is due to the anatomy of the female pelvis. The sacrum and coccyx are located much more posteriorly and the ischial tuberosities are farther apart in women than in men (figures 1 and 2) because the pelvis must accommodate a baby's head during birth. Both of these anatomic factors leave a woman's coccyx exposed and susceptible to trauma. Acute trauma, such as the fall in the sitting position which this patient sustained, is the most common etiology of coccydynia. Birth trauma is another common cause of acute coccydynia; some patients even fracture the coccyx during a difficult delivery. Our patient had an acute coccyx injury as well as repeated minor trauma to the coccyx when sitting with her feet propped up, which shifts her weight from her ischial tuberosities and thighs to her coccyx.

Our patient's history of anxiety and depression is worth noting. Some clinicians have found a preponderance of patients with psychologic problems among those with coccydynia. Wein[3] concluded that coccygeal pain may be part of a chronic pain syndrome caused by hysterical neurosis, although others disagree.[2]

Diagnostic evaluation begins after obtaining a suggestive history and includes a thorough physical examination. The coccyx should be tender to palpation. Rectal and pelvic exams are necessary to exclude rare causes of coccygeal pain such as pelvic infection or tumor. A pelvic ultrasound can help exclude a pelvic mass but is not always necessary. Close follow-up demonstrating a benign course confirms the diagnosis.

Treatment in the acute phase consists of hot sitz baths and nonsteroidal anti-inflammatory drugs. Thereafter, therapy is directed toward protecting the coccyx from further trauma by having the patient sit erect on a doughnut or

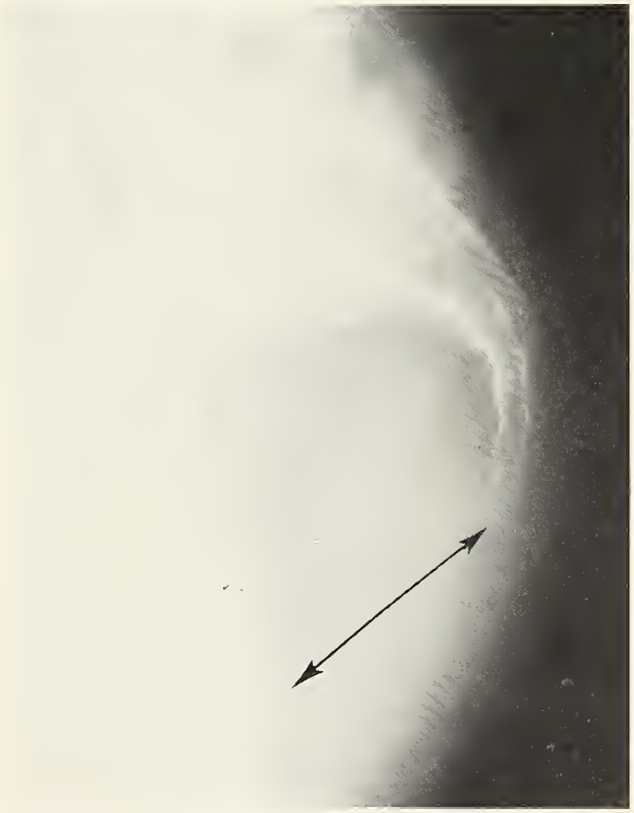

Figure 1. *Lateral coccyx x-ray of Case 1, a 39-year-old woman with coccydynia. Arrows indicate the posterior, exposed position of the coccyx normally seen in women.*

From the Division of General Medicine, Duke University Medical Center, Durham 27710.

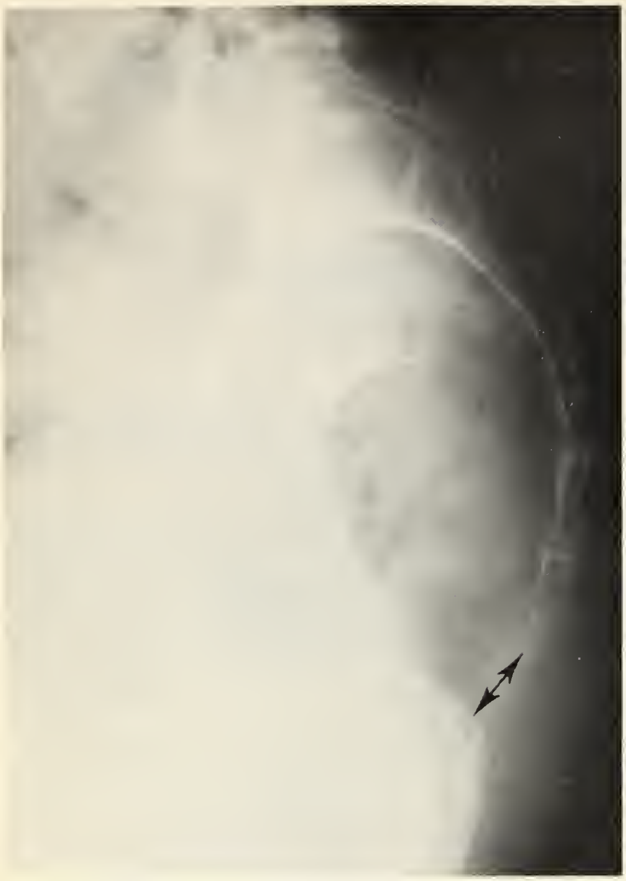

Figure 2. *Lateral coccyx x-ray of 36-year-old man without coccydynia. Arrows indicate the more protected anterior position of the coccyx normally seen in men.*

U-shaped pillow. Most patients have complete resolution of symptoms within six months, as is illustrated by the next case.

Case 2

A 52-year-old unmarried teacher developed intermittent pain in her "tailbone" over a two month period. It was worse on sitting but there was no dysuria, vaginal discharge or pain with defecation. She was not sexually active. After a bus tour of the Southwestern United States she presented for evaluation. Height was 5′4″ (162.6 cm), weight was 114 lbs (51.3 kg); she appeared healthy. There was exquisite coccyx tenderness on palpation both externally and internally during the rectal examination. Pelvic examination was normal; there was no rectal mass; stool was guaiac negative. Coccyx x-rays were unremarkable. The patient was relieved to hear that her examination was normal. She used a foam rubber doughnut and naproxen 250 mg by mouth twice daily. The pain resolved over the next month and she has been pain-free during five months of follow-up.

Comment: Subacute trauma, usually not recognized as such by the patient, is the second most common etiology of coccydynia. This patient probably traumatized her coccyx during her long bus ride. A complete history and physical examination excluded any worrisome pathology and the diagnosis was confirmed by careful follow-up. This patient was at particular risk for coccydynia because she is so thin. Pilonidal cyst or infections, such as salpingitis or perirectal abscess, can cause coccydynia, but our patient was not at risk for sexually transmitted disease, and pelvic and rectal examinations were normal. Proctalgia fugax can mimic coccydynia, but these patients will have no coccyx tenderness on examination.

Levator ani spasm can contribute to coccydynia and has been treated with digital massage through the rectum, or injection of local anesthetic with or without cortisone.[3, 4] Surgical removal of the coccyx was frequently performed during the nineteenth and early twentieth centuries,[2] but is rarely used today because simple conservative measures such as a foam doughnut and analgesics are usually sufficient to relieve coccygeal pain.

Case 3

A 22-year-old medical student developed coccygeal pain shortly after riding his motorcycle from Houston to Mexico City and back, a distance of 2000 miles (3225 km). Physical examination revealed coccyx tenderness but was otherwise unremarkable. He was advised to sit on a pillow, but only complied during the evening because he was embarrassed to carry a pillow to class. He continued to ride his motorcycle against his physician's advice. Ultrasound treatments did not relieve his pain, and an injection of local anesthetic made it worse. The pain persisted for 9 months; he sold his motorcycle and in 14 years of follow-up he has not had a recurrence.

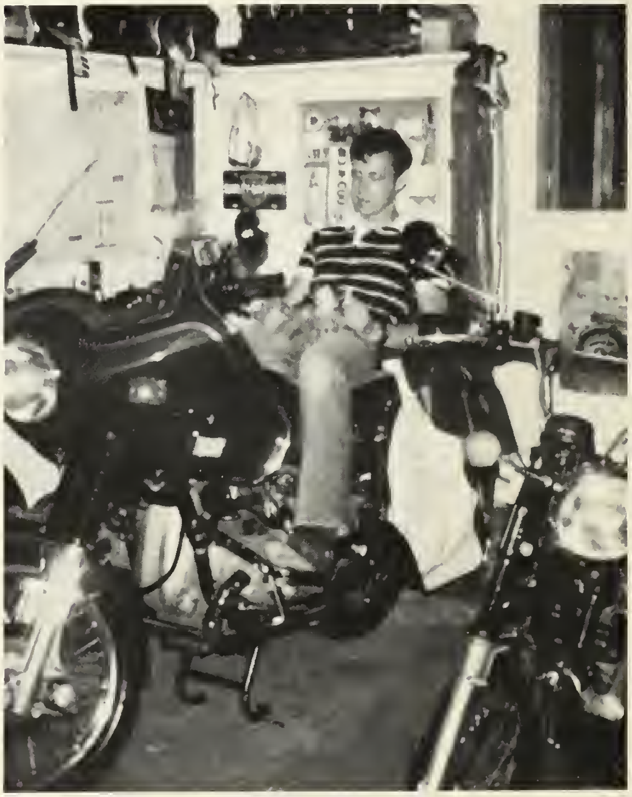

Figure 3. *Case 3, a 22-year-old man with coccydynia from motorcycle riding. The slumped sitting posture exacerbates the condition by shifting weight from the ischial tuberosities and thighs onto the coccyx.*

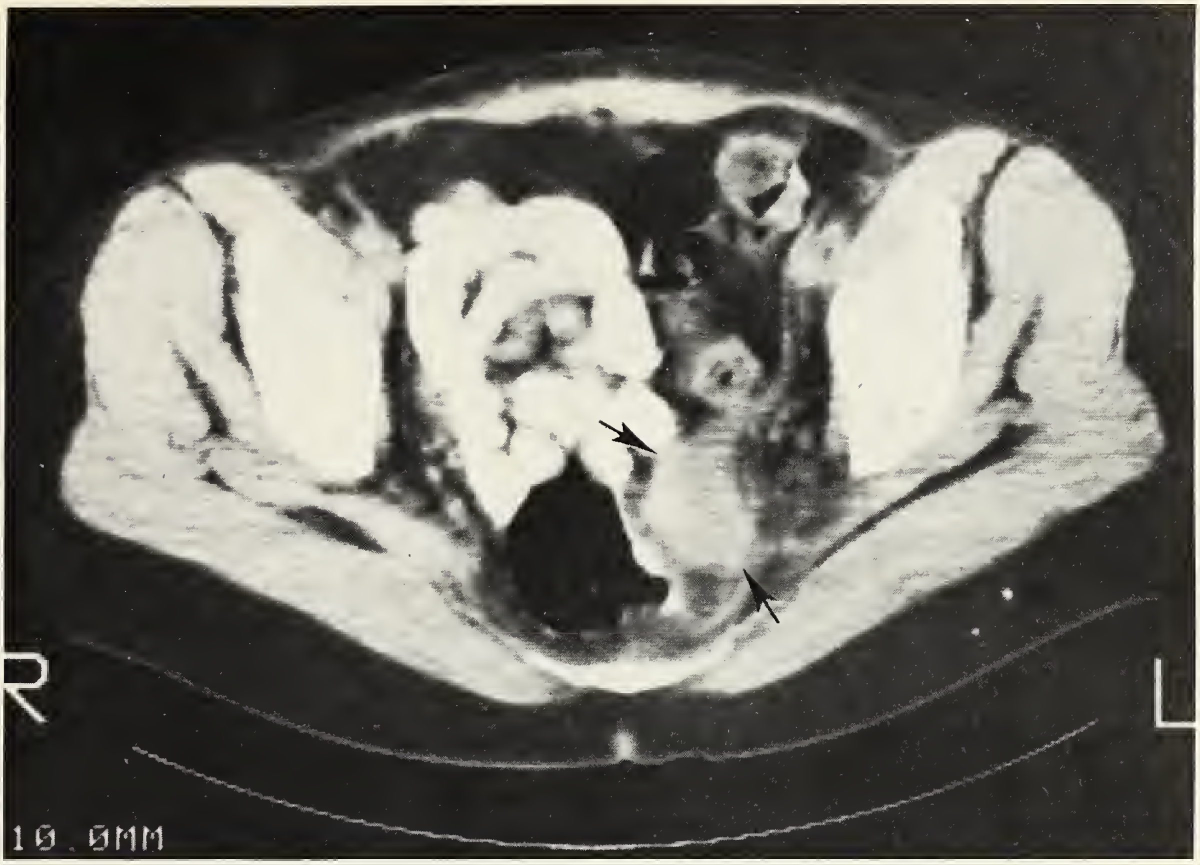

Figure 4. *Computerized tomography of the pelvis from Case 4. Arrows indicate the presacral mass due to metastatic endometrial cancer which caused coccydynia by nerve root involvement.*

Comment: In men with coccydynia, acute and chronic coccyx trauma can usually be identified. This patient sustained repeated blows to the coccyx from his motorcycle seat; men who ride tractors, jeeps or snowmobiles are also at risk.[4] Poor sitting posture contributes to the condition. This patient sat for long periods of time because he was a medical student, and he often sat in a slumped position (figure 3), producing direct pressure on the coccyx. Prolonged sitting while watching television can exacerbate coccyx pain, so one author has called coccydynia "television bottom."[4]

Most patients with coccydynia have a short-lived or benign intermittent course, but rarely a patient will present with more serious pathology, as is illustrated by the following case.

Case 4

A 50-year-old woman reported that she had fallen and dislocated her coccyx 20 years ago; she had improved spontaneously within several weeks. She was asymptomatic until four weeks prior to evaluation when she noticed the insidious onset of severe pain in her coccyx. There was no known trauma to the region but her job required that she sit for long periods. On examination there was tenderness at the sacro-coccygeal junction; no mass, redness or swelling was seen. On rectal examination movement of the coccyx induced pain but no mass was noted. Coccyx x-ray showed her old dislocation; bone scan was normal. She was advised to use a rubber doughnut and ibuprofen which helped minimally. Over the next two months the pain became increasingly severe. A repeat pelvic and rectal examination revealed a 2 cm tender, firm area along the left sacral prominence. Computerized tomography of the pelvis showed a left presacral mass (figure 4). Exploratory laparotomy revealed metastatic endometrial carcinoma invading the sacral plexus. After this lesion was removed the coccyx pain resolved. Unfortunately, the patient had a progressive downhill course and died nine months later.

Comment: Primary tumors involving the coccyx are extremely rare. Bone can be destroyed by cordomas or giant cell tumors; nerve tissue can be involved in ependymomas or glomus tumors of the cauda equina. Tumors of the pelvic organs as well as malignant melanoma and cancer metastatic from other sites should be suspected if coccygeal pain is markedly severe and unrelenting.[3] In such cases, pelvic and rectal examinations should be repeated and ultrasound or computerized tomography should supplement the clinical examination.

Plain coccyx x-rays are not helpful in most patients with coccydynia: in one series, coccyx x-rays were nondiagnostic in 95% of cases.[1] Plain films are primarily useful for detecting a fracture or dislocation; an enema to remove rectosigmoid stool prior to x-ray will give the best visualization of bony structures. In our patient, the plain films were unremarkable even though a tumor was present.

Summary

When the patient presents with a painful tailbone, the doctor should suspect that there is a small chance of malignant or infectious pathology. A good history and physical examination with close follow-up will generally rule out more serious disorders. When treated with proper posture, a doughnut cushion to relieve coccygeal pressure and a nonsteroidal anti-inflammatory agent, pain will improve or resolve within several months. If pain is progressive or unrelenting, further investigation is required.

Acknowledgment

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INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli*, *P. mirabilis*, *Klebsiella* species, and enterococci (*S. faecalis*).

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

Other antibacterial agents — Bacteriostats may interfere with the bactericidal action of cephalosporins in acute infection; other agents, e.g., aminoglycosides, colistin, polymyxins, vancomycin, may increase the possibility of nephrotoxicity.

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Pediatric Use: Adequate information is unavailable on the efficacy of b.i.d. regimens in children under nine months of age.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

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DOSAGE: Adults — For respiratory tract infections (other than lobar pneumonia) and skin and skin structure infections: 250 mg q. 6 h or 500 mg q. 12 h. For lobar pneumonia: 500 mg q. 6 h or 1 g q. 12 h. For uncomplicated urinary tract infections: 500 mg q. 12 h; for more serious UTI, including prostatitis, 500 mg q. 6 h or 1 g q. 12 h. Severe or chronic infections may require larger doses (up to 1 g q. 6 h). For dosage recommendations in patients with impaired renal function, consult package insert.

Children over 9 months of age — 25 to 50 mg/kg/day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae*: 75 to 100 mg/kg/day in equally divided doses q. 6 or 12 h but not to exceed 4 g/day. Dosage for children should not exceed dosage recommended for adults. There are no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

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SCIENTIFIC ARTICLE

The Bedside Evaluation of Orthostatic Hypotension

Scott R. Brazer, M.D.

- *Simple, readily available bedside tests can narrow the differential diagnosis of orthostatic hypotension with little expense to the patient.*

WITHOUT a functioning baroreflex arc to maintain cerebral perfusion upon assumption of the upright posture, presyncope and syncope result. Patients with lesions at any point in that arc come to medical attention because of orthostatic hypotension.* In the 40 years since Dr. E. A. Stead Jr.'s review,[2] the differential diagnosis facing the clinician has become so extremely large that indiscriminate and expensive testing may result.

Case 1

A 35-year-old woman referred for evaluation of disabling orthostatic hypotension, had a supine blood pressure of 108/72 with a pulse of 100 while her standing blood pressure was 70 by palpation with a pulse of 160. The remainder of her physical exam was normal. The following studies, suggested by numerous consultants, were either "negative" or normal: rectal biopsy; sigmoidoscopy; upper GI with small bowel follow through; myelogram; liver spleen scan; brain CT; chest x-ray; urine metanephrine/VMA; serum protein electropheresis; lumbar puncture (×2); serum cortisols; angiotensin converting enzyme; toxin screen; chem 18; thyroid panel; FANA (×2); CBC; urinalysis; VDRL (×3); sputum AFB culture; urine Bence Jones protein; urine porphyrins; stool porphyrins; urine porphobilinogen; free erythrocyte protoporphyrin (the latter four tests ordered after a false positive screen); urine for heavy metals; and 48 hour ACTH stimulation test. Hospital costs exceeded $20,000. Yet the cause of her disorder was not clarified. She was discharged wearing a Jobst garment, eating a high sodium diet, and taking fludrocortisone but was able to walk only short distances with assistance.

The first issue to address in patients who present with orthostatic hypotension is whether the baroreflex arc (figure 1) is intact and if not which component is not functioning properly. The integrity of the entire system and the function of the individual components may be sequentially examined, much as an electrician tests a faulty circuit, giving appropriate direction to the subsequent diagnostic work-up. The elaborate or invasive testing of these patients, characteristic in the 1940s-1960s, may be avoided in most clinical settings and can be replaced by simple bedside maneuvers. Although intravascular recordings are more accurate in determining blood pressure, noninvasive monitoring is preferred because of increased patient comfort, elimination of risks, decreased cost, and because it does not cause the marked alterations in response of the baroreflex arc to orthostatic challenges, seen with intravascular monitoring.[3]

The integrity of the entire circuit can be tested with an electrocardiogram (ECG) rhythm strip and two simple maneuvers.

Paced Respiration. The patient breathes deeply at a rate of six times a minute. A normal response is defined as an

BAROREFLEX ARC

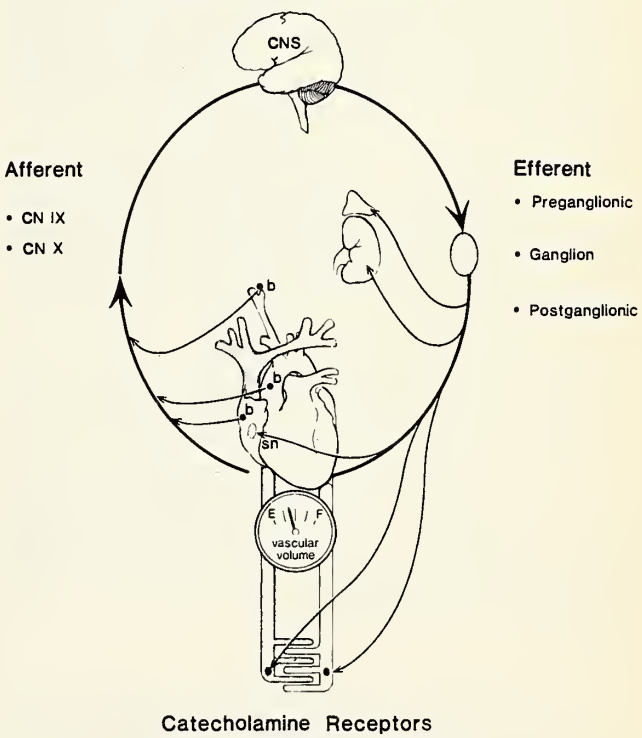

Figure 1. *The baroreflex arc.*

From the Department of Medicine, Duke University Medical Center, Durham 27710.

* Arbitrarily defined as a systolic BP decrease of 30 or a diastolic BP decrease of 15 recorded at one and two minutes after assuming an upright posture in a symptomatic patient.[1]

increase in pulse of greater than 15 on inspiration; an abnormal response results in an increase of less than 10 beats per minute.[4]

Valsalva Index. The Valsalva maneuver has four phases, the first two during strain and the second two after release: I. increased blood pressure secondary to increased intrathoracic pressure upon the aorta; II. decreased blood pressure and resultant tachycardia secondary to decreased venous return and cardiac output; III. further decrease in blood pressure and tachycardia secondary to release of intrathoracic pressure on the aorta; IV. so-called "overshoot" of blood pressure with bradycardia secondary to vasoconstriction induced in phases II and III.

While the ECG is being recorded, the patient performs a Valsalva maneuver by blowing the mercury column of a sphygmomanometer to 40 mm Hg for 15 seconds. The ratio of the longest RR interval in phase IV (after release) divided by the shortest RR interval in phase II (before release) should be greater than 1.2. A ratio less than or equal to 1.1 is considered abnormal.[4]

If these tests are normal, the individual's reflex circuit is intact. Such patients have postural tachycardia as well as elevated catecholamine levels and have sympathicotonic orthostatic hypotension or intravascular volume depletion (technically a secondary form of sympathicotonic orthostatic hypotension).

Sympathicotonic orthostatic hypotension occurring in euvolemic patients is a result of an insufficient increase in the vascular bed's tone. The cause of the primary form, usually a disease of young females, remains unknown. Secondary sympathicotonic orthostatic hypotension occurs in patients with severe illness typically from infection or with profound electrolyte disturbances.

If any of the screening tests are abnormal, the circuit is not intact. These patients have hypoadrenergic orthostatic hypotension and commonly have other features of autonomic insufficiency such as impotence, decreased sweating and loss of premonitory signs prior to a faint. Their prognosis is less favorable than patients who have an intact reflex arc.[5]

One can bypass the afferent limb and test the efferent limb in such a patient by the cold pressor test. Placing that individual's hand in ice water for one minute should cause a rise in systolic blood pressure greater than 15 mm if the efferent limb is intact.[6] A normal response then implies an afferent limb defect.

If the cold pressor test is abnormal, the efferent limb is defective. Postganglionic lesions can be defined by their resultant denervation hypersensitivity. For example, instillation of 1 or 2 drops of 1 : 1000 epinephrine into the eye of such a patient often produces marked dilation whereas this dose would lead to no significant pupillary change in normal individuals. In addition, patients with postganglionic defects have low plasma norepinephrine levels, another aid in distinguishing them from those with preganglionic efferent defects.

Case 2

A 57-year-old man who had recently undergone resection of a posterior fossa astrocytoma presented with presyncope due to orthostatic hypotension. Supine blood pressure was 174/120 with a pulse of 76 while standing blood pressure was 94/70 with a pulse of 84. He had an abnormal response to paced respiration (pulse change of 6); an abnormal Valsalva Index (1.0); and the cold pressor response was absent (figure 2). These findings localized the defect to the efferent limb, consistent with a preganglionic lesion resulting from prior surgery and the tumor per se. Therefore, no further diagnostic testing was necessary. In this instance the evaluation took less than 15 minutes with a cost of only $20 for the ECG.

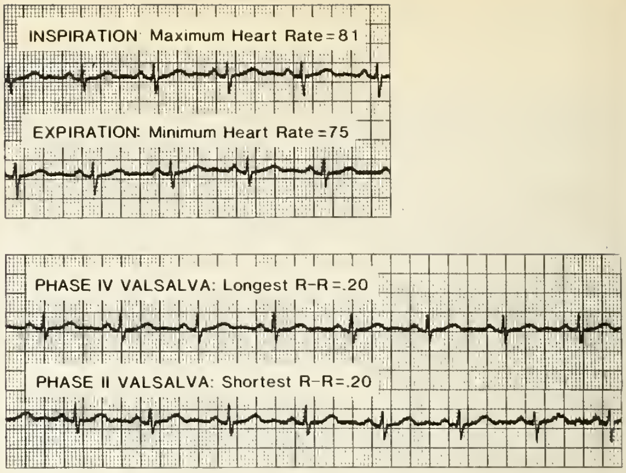
INSPIRATION: Maximum Heart Rate=81
EXPIRATION: Minimum Heart Rate=75
PHASE IV VALSALVA: Longest R-R=.20
PHASE II VALSALVA: Shortest R-R=.20

Figure 2. *Results of paced respiration and Valsalva Index in case 2.*

Later re-evaluation of our first patient after the initial exhaustive studies, showed an intact reflex circuit manifest by normal responses to Valsalva and paced respiration. One could have eliminated from the differential those diseases which result in destruction of the baroreflex arc from these screening tests alone. The etiology of her illness was still unknown 3 years after the onset, when she had recovered sufficiently to return to work. She is typical of patients with primary sympathicotonic orthostatic hypotension.

Treatment

Whenever possible, the underlying disorder should be treated. When that is not feasible or doesn't eliminate the patient's symptoms, the next step should consist of mechanical maneuvers which are relatively inexpensive and carry little risk. Patients should be instructed to rise slowly from a supine or sitting position. Sleeping with the head of the bed elevated may activate the renin-angiotensin system, thereby decreasing the amount of venous pooling that ordinarily occurs upon arising. An elastic garment, properly fitted from the metatarsals to the costal margin, is frequently helpful. Bannister[7] has described the vicious cycle of orthostatic hypotension in which forced inactivity leads to further deterioration of the baroreflex arc. This phenomenon might be prevented by the use of a conservative exercise program when tolerated by the patient.

The pharmacologic approach to treatment includes volume expanders and vasoconstrictors, recognizing that these methods may precipitate recumbent hypertension or congestive heart failure. Cautious use of high sodium diets with fludrocortisone should be attempted in patients who do not have contraindications. Remember, the recumbent hypertension induced by these agents can result in increased cerebrovascular resistance and thereby might aggravate symptoms of cerebral ischemia when assuming an upright posture.[8] Single case reports and collected series have suggested benefits from a variety of drugs including: ephedrine, vasopressin, tyramine, ritalin, amphetamines, phenylephrine, MAO inhibitors, dihydroergotamine, midodrine, inderal, pindolol, indomethacin, clonidine, yohimbine and metoclopramide.[2, 6-9] These agents have not met with widespread or lasting success and are often harmful.[7] They should therefore be prescribed only by those familiar with their use and with the need for serial observation since long-term complications often outweigh transient improvement.

Conclusion

The differential diagnosis of orthostatic hypotension is broad but can be narrowed with readily available and easily performed bedside tests (figure 3). Such an algorithm aids in the assessment of patients with the problem, and when the etiologic diagnosis is not readily apparent the subsequent work-up can be focused more precisely. An ECG, sphygmomanometer, bucket of ice, and some epinephrine ophthalmic solution are all that is needed to guide the evaluation and assign the disorder to a specific component of the baroreflex arc.

Difficulty may arise when employing this schema in patients who have lesions in more than one location. Most patients with idiopathic orthostatic hypotension have been noted to have their predominate lesion in the postganglionic efferent limb; but abnormalities of the afferent limb, preganglionic efferent limb and catecholamine receptor have been described. Diabetics may have orthostatic hypotension secondary to involvement of the afferent limb and baroreceptor, postganglionic efferent limb, or due to intravascular volume depletion.[10]

Patients with lesions involving the CNS or the vascular bed are confusing because our understanding of their role in blood pressure regulation is incomplete. With the development of centrally acting antihypertensives,[11] the CNS circuitry is becoming clearer. The afferent pathway of the baroreflex arc leads to the nucleus tractus solitarius in the floor of the fourth ventricle. Axons from this area run to the rostral ventrolateral medulla which acts as the vasomotor center. Its neurons synapse with the preganglionic efferent neurons in the intermediolateral column of the thoracic cord. As our understanding of the central nervous components improves, disturbances of them may be more accurately correlated with specific clinical diagnoses.

Orthostatic hypotension occurring in patients with an intact reflex arc is due to an inadequate response by the vascular bed to either the hyperadrenergic state or hypovolemia. One term for this is sympathicotonic orthostatic

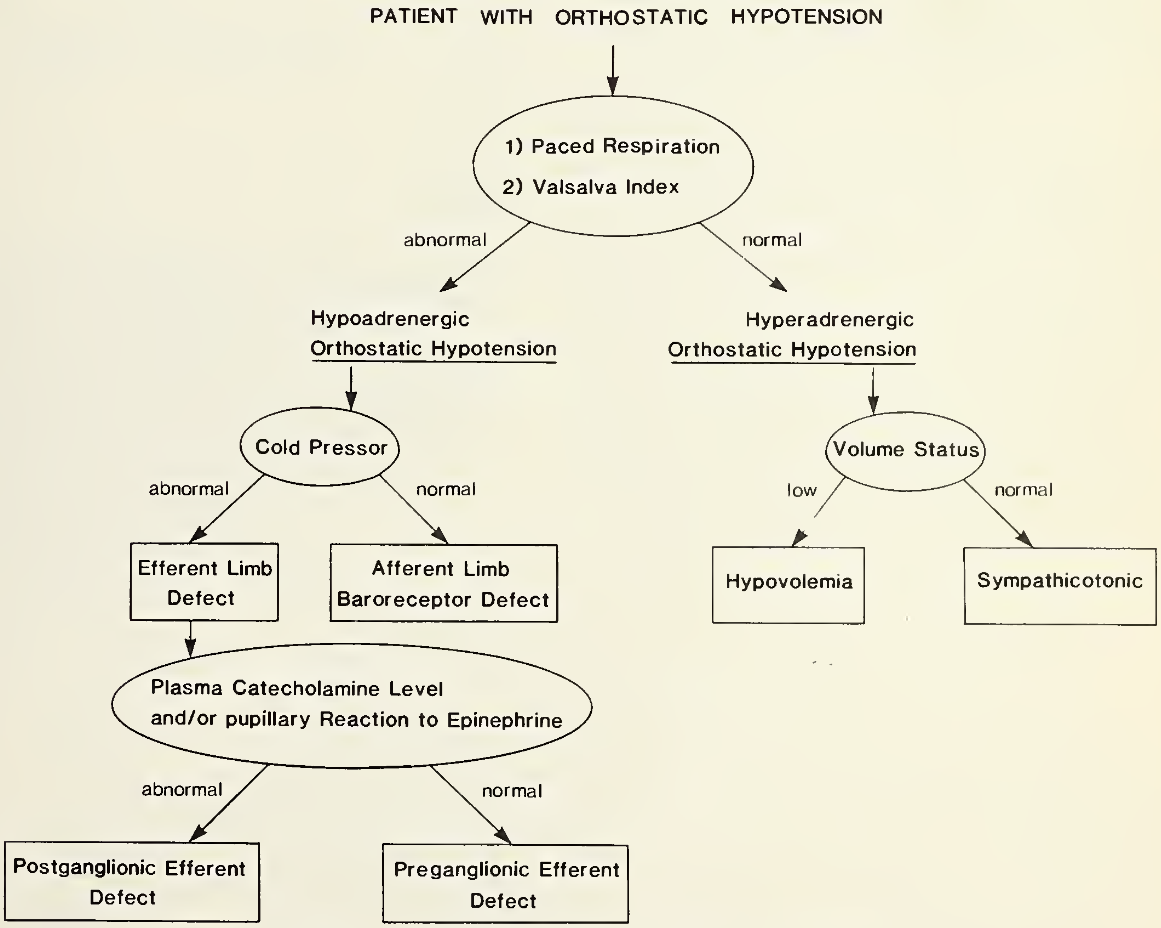
PATIENT WITH ORTHOSTATIC HYPOTENSION
1) Paced Respiration
2) Valsalva Index
abnormal
normal
Hypoadrenergic Orthostatic Hypotension
Hyperadrenergic Orthostatic Hypotension
Cold Pressor
abnormal
normal
Volume Status
low
normal
Efferent Limb Defect
Afferent Limb Baroreceptor Defect
Hypovolemia
Sympathicotonic
Plasma Catecholamine Level and/or pupillary Reaction to Epinephrine
abnormal
normal
Postganglionic Efferent Defect
Preganglionic Efferent Defect

Figure 3. *Algorithm for evaluation of orthostatic hypotension.*

Table 1
Differential Diagnosis of Orthostatic Hypotension

Hypoadrenergic (arc not intact)	Hyperadrenergic (arc intact)
Postganglionic Efferent Defect	Sympathicotonic
1. Neuropathies (i.e., alcohol, diabetes)	1. Primary
2. Idiopathic orthostatic hypotension	2. Secondary
3. Sympathectomy	a. severe illness
4. Sympatholytic drugs	b. electrolyte abnormalities
Preganglionic Efferent/Central Defect	Hypovolemia
1. Destructive lesions (i.e., CVA, tumors)	1. Absolute (i.e., Addison's)
2. Centrally acting drugs	2. Relative
3. Riley-Day syndrome	a. vasodilating drugs
4. Shy-Drager syndrome	b. endogenous vasodilators
Afferent/Baroreceptor Defect	1) pregnancy
1. Diabetes mellitus	2) hyperbradykinism
2. Alcohol	c. varicose veins
3. Hemodialysis related	d. prolonged bedrest
4. Holmes-Adie syndrome	e. pheochromocytoma
5. Tabes dorsalis	

hypotension. A primary form occurs as an idiopathic disorder most commonly affecting young women. Secondary forms are seen in patients with severe co-existent illness or hypovolemia. It is not difficult to understand the clinician's pursuit of a treatable condition in an otherwise healthy young patient disabled by orthostatic hypotension; however, demonstration of an intact reflex arc allows this search to be confined to those entities that cause orthostatic hypotension without destruction of the circuit (table 1).

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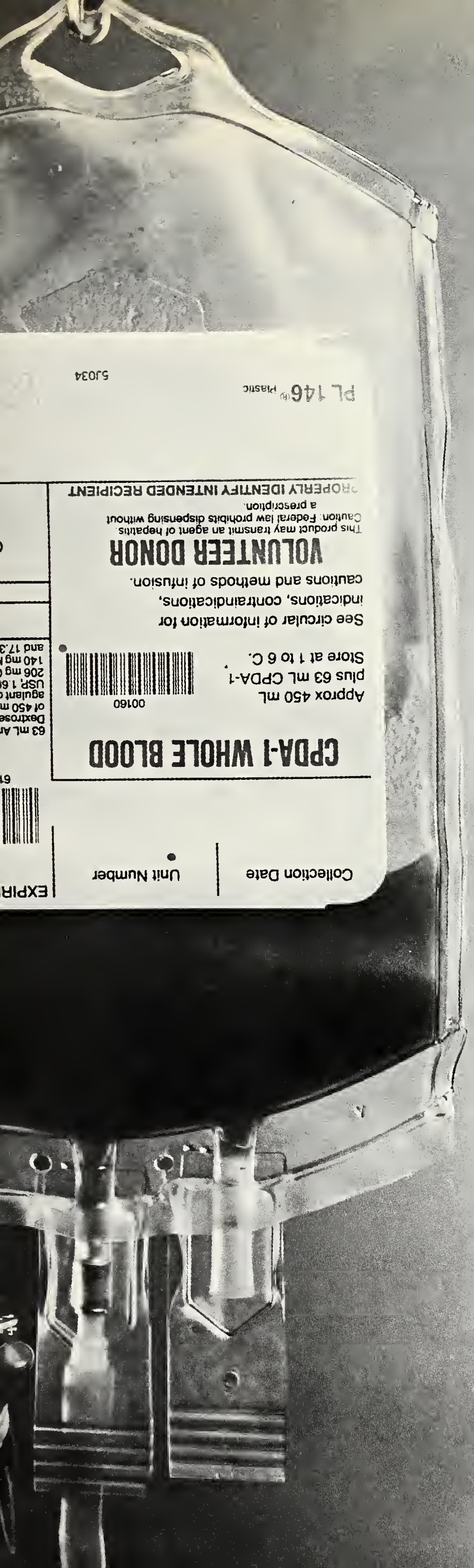

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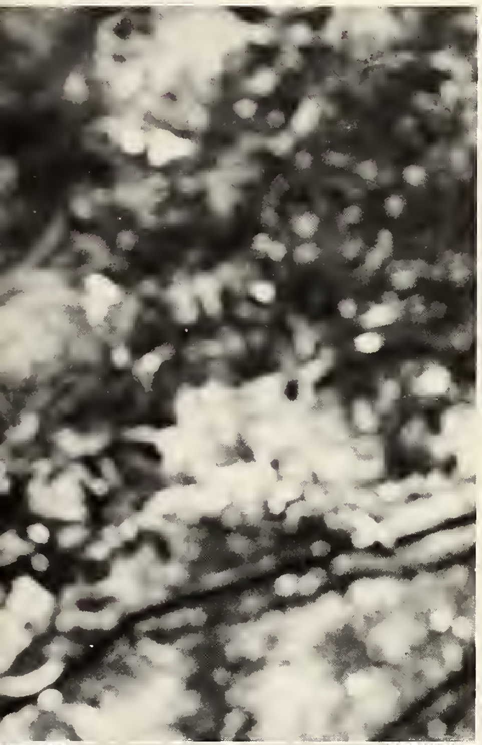

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Premenstrual Syndrome

John F. Steege, M.D., Anna L. Stout, Ph.D., Sharon L. Rupp, R.N.C.

Recently much attention has been given to an age-old problem: the changes that many women experience premenstrually. When these changes are more severe, they have been called "premenstrual syndrome" or "PMS." These pages will review what PMS is, how women can help themselves with the symptoms, and what kind of medical help can be most useful.

PMS — The Problem

Many women experience some feelings of breast tenderness, greater or lesser degrees of symptoms from fluid retention, and some feelings of emotional change. Many also experience positive feelings of increased energy, greater sensitivity both emotionally and artistically, and greater creativity for a week or two prior to the beginning of the menstrual flow.

From ancient times medical writers have described some of the more negative aspects of these changes and have puzzled over the causes. The impact of the menstrual cycle on the human body is profound. Approximately 65 well-recognized medical diseases and 115 normal events in the body's physiologic makeup have been shown to be influenced by the menstrual cycle. It is no wonder, then, that women who experience severe changes premenstrually may notice a wide variety of symptoms. Approximately 150 symptoms have been described at one time or another as being related to the menstrual cycle.

The symptoms of PMS can be grouped as shown in table 1. Our experience tells us that women who experience more severe emotional changes premenstrually do not necessarily experience physical changes that are more severe than other women. Rather, they find emotional changes extremely disturbing and disruptive in their personal relationships and their ability to function at work and home.

Although a great deal of research has been done, no one has really discovered the cause of PMS. Most people agree that it is a "real" illness, that definite chemical and physical changes are involved with PMS symptoms, but the exact nature of those changes is unclear. Many others have recognized, however, that a person's individual personality and the stresses to which that person is exposed may have strong influences on the severity of PMS symptoms.

This complex disorder deserves a most careful evaluation in order to bring about the best results from any kind of treatment.

Making the Diagnosis

Many women can simply think back in time and accurately remember that every time their period approaches they will feel irritable and somewhat depressed. When they write down these events on a calendar the pattern is often confirmed.

However, when a person is troubled with significant premenstrual symptoms, making the diagnosis is often more difficult due to the way our memories work. When two events happen together, it is easier for a person to remember them than to recall similar events that occur singly. For instance, if someone has a migraine headache during the menstrual flow it has been shown that it is easier for her to remember those events together than it is to remember migraine headaches that may happen at other times in the cycle, when nothing else is going on.

For these reasons, most doctors or clinics working with PMS find it best to first find out what a woman's major symptoms are and then have her chart those symptoms on a daily basis using one type of calendar or another. She can then bring these calendars to the next visit with the doctor and examine them to see how much of the difficulty she is experiencing follows a premenstrual pattern. The doctor should also perform a thorough physical examina-

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Table 1
Common Symptoms of Premenstrual Syndrome

- **Affective**
  - Sadness
  - Anxiety
  - Irritability
  - Labile mood
- **Pain**
  - Headaches
  - Breast tenderness
  - Joint and muscle pain
- **Autonomic**
  - Nausea
  - Diarrhea
  - Palpitations
  - Sweating
- **Fluid**
  - Bloating
  - Weight gain
  - Decreased urination
  - Swelling
- **Behavioral**
  - Decreased motivation
  - Poor impulse control
  - Decreased efficiency
  - Social isolation
- **Cognitive**
  - Decreased concentration
  - Indecision
  - Paranoia
  - Sensitive to rejection
  - Suicidal ideation
- **Neurovegetative**
  - Insomnia
  - Hypersomnia
  - Anorexia
  - Craving for certain foods
  - Fatigue
  - Lethargy
  - Agitation
  - Libido change
- **Central Nervous System**
  - Clumsiness
  - Seizures
  - Dizziness
  - Vertigo
  - Paresthesias
  - Tremors
- **Dermatological**
  - Acne
  - Greasy hair
  - Dry hair

From Rubinow DR, Roy-Byrne P. Premenstrual syndromes: overview from a methodologic perspective. Am J Psychiatry 1980;141:163-72.

tion to look for other medical illnesses that might influence a person's general feeling of well-being as well as perhaps be responsible for symptoms similar to PMS. Some screening blood tests to look for various kinds of medical illness are also useful. No one yet has discovered any single blood test to diagnose PMS. Various hormone levels including progesterone levels are useful in deciding whether the menstrual cycle is normal in certain ways, but none of them is accurate in diagnosing premenstrual syndrome.

There are several gynecologic conditions that can perhaps contribute to some of the symptoms of premenstrual syndrome, especially the lower abdominal and pelvic cramping and aching. These include endometriosis, large fibroids in the uterus, and a condition called andenomyosis which can cause some enlargement or swelling of the uterus. Often these problems can be detected on a regular pelvic examination, but they sometimes require a laparoscopy for confirmation. This minor surgical procedure, done under anesthesia, allows the doctor to look inside the pelvic area.

PMS can occur at any age after menstruation has begun. However, women are often most severely affected during their 30s and 40s. Although many clinicians have wondered whether such things such as having children, taking birth control pills, or having menstrual cramps (dysmenorrhea) influence women's tendencies to get PMS, most of these ideas have not been confirmed by research so far. For example, there is no credible evidence that taking birth control pills aggravates premenstrual symptoms with any regularity, nor do they make a person more likely to get severe PMS symptoms after discontinuing the pills. Similarly, although some women will note the beginning of PMS symptoms after childbirth, most do not seem to follow that pattern, or any other pattern relating events in reproduction (sterilization, etc.) to the beginning of PMS symptoms. It has been said that menstrual cramps are seldom present in women with PMS. Our experience has been quite contrary to this; we find that many women with more severe PMS also have more severe menstrual cramps. These examples are important to keep in mind since they demonstrate that we really need to know a lot more about premenstrual syndrome.

Another extremely important area in the evaluation of PMS is an assessment of an individual's overall personality and the stress that she might be experiencing in day-to-day life. We are just beginning to learn about the ways in which stress can affect a person both physically and psychologically, and we have known for many years that stressful things can influence the menstrual cycle in very profound ways, such as stopping the cycle altogether, or sometimes preventing the release of an egg from the ovary (ovulation). Often progress made in reducing the effect of the stresses in one's life can also bring about significant improvement in PMS symptoms.

Many doctors ask their patients with PMS to undergo some form of psychological evaluation for these reasons. This might involve psychological testing and almost always involves some kind of interview with someone experienced in the mental health or counseling field.

Causes and Treatments of PMS

We will discuss the causes and treatments of PMS together, since various ideas about causes have logically led to suggestions about how to treat the problem.

It is important to know that it is very difficult to prove that a particular medication or treatment is effective because of the very complex nature of the problem. Since there are no blood tests to follow to look for improvement, we must rely on reports of changes in symptoms, many of which are internally perceived and cannot be observed by someone other than the person affected. For these reasons, most studies looking at drugs in the treatment of PMS will notice that anywhere between 25% and 50% of women will notice some improvement even with a placebo or "sugar pill" medication.

Another major factor in the difficulty in finding a "cure" for PMS is that it seems that combinations of treatments very often work better than any single treatment by itself. This makes it very difficult for researchers to figure out which might be the most important "ingredient" in a treatment. Nevertheless, we will review the treatments most often used and discuss their value.

Nutrition

Many women complain of distinct food cravings during their premenstrual time. Usually these are for sweet foods including such things as chocolates, cake, bread, and other carbohydrates. There is some evidence that the body handles these products differently premenstrually than it does at other times. Diabetics more often have trouble regulating their disease during this time and insulin production is somewhat different premenstrually in women without diabetes. There is some thought that hypoglycemia, or the tendency of the blood sugar to drop down to a low level in a rebound fashion after a meal high in sugar, is more common in people with premenstrual syndrome.

Although nutrition in PMS remains incompletely investigated, there is some evidence to suggest that people with premenstrual syndrome symptoms in fact eat a less well balanced diet than those without symptoms. For these reasons we and others have found it useful to suggest certain dietary modifications to treat PMS.

We suggest that a person eat a diet with a normal protein level, with only small amounts of foods with high sugar content and refined carbohydrates. The "refined" carbohydrates are most commonly seen in white flour products and sweet foods in general. In addition, it is good to avoid chocolate because of both its high sugar content and its caffeine level.

Chemicals that stimulate the brain are also thought to increase irritability premenstrually, especially substances such as caffeine. Using decaffeinated beverages is often helpful.

Although many women report feelings of bloatedness premenstrually, careful study has failed to document significant weight gain premenstrually in most women. For this reason, we discourage the use of diuretics or fluid pills, but do find it useful for a person to be careful about avoiding excess sodium intake during the premenstrual time. This would mean avoiding salty foods such as preserved meats (bacon, sausage, ham, etc.), commercial vegetable products with salted sauces, broth soups, potato chips, etc.

Considerable attention has been paid to the role of micronutrients or chemicals that are present in small amounts in our diets. We generally recommend a single multivitamin/multimineral supplement that is available in many forms at the vitamin counter of the drug store. There is no good proof that special supplements high in such things as zinc and magnesium have any additional benefit in treating premenstrual symptoms.

Vitamin supplements are frequently recommended for PMS. Vitamin B_6, or pyridoxine, has been known for many years to be an important factor in many chemical reactions in the body including those involving sugars as well as many brain chemicals thought to influence mood. In addition, good studies show that vitamin B_6 will relieve depression symptoms in a significant number of women experiencing these problems while taking birth control pills. For these reasons vitamin B_6 has been used to treat PMS. There are several studies to show it is effective. Most studies have used vitamin B_6 at 100 mg per day and for this reason we stick to this dose level. There is real concern about toxicity to the nerves, that is, problems with decreased sense of balance and touch, in people who use more than 2,000 mg daily. Although there is no evidence suggesting toxicity at lower doses, we have maintained the 100 mg per day limit out of caution. When a person uses vitamin B_6 supplements it is useful to use a general vitamin B complex supplement as well.

Vitamin E has been described as helpful for the treatment of breast pain premenstrually as well as for relief of pain from fibrocystic changes in general. Although there is again some confusion in this area many physicians do feel it useful at a dose of about 400 units per day.

Exercise

Much research has been done recently about the effects of exercise on brain function and mood in general. Good studies show that it is effective in treating simple forms of depression, and other reports indicate that it helps the symptoms of premenstrual syndrome as well.

Researchers have speculated that exercise changes the levels of brain chemicals called endorphins and that this may be important in both the regulation of mood and the perception of pain. For these reasons, as well as for the general feeling of well-being that exercise often provides, we suggest regular daily exercise for women experiencing PMS.

For many women PMS symptoms become most bothersome during stressful times. Often this means that they feel unable to fulfill all their responsibilities at work and at home. This is just the time when a prescribed break of even as little as 15 minutes or one-half hour per day for a walk is very useful for coping with stress.

Exercise may also help combat the effects of sleep disturbance that sometimes appear premenstrually.

Altered sleep patterns that accompany PMS and depression may be the cause of some general muscle aches and pains and stiffness that people often report.

Finally, daily exercise will help with weight reduction. Some doctors feel that PMS symptoms are worse for women significantly over their ideal weight.

Lifestyle

Of the problems reported by our patients, the most common is the feeling of not being able to cope with ordinary demands. One of the most helpful things about charting one's own symptoms is that it becomes possible to predict on which days the most difficulties will be encountered. With this in mind, it may be possible to schedule some optional activities that are stressful for the times when the fewest symptoms are present. Certainly, this is not always possible, but to whatever degree it can be done, this plan can certainly be helpful.

One of the easiest suggestions to make, but perhaps one of the hardest to follow, is to allow a bit of time for yourself, even on the most stressful days. Whether this is in the form of simply being alone, having the time for a leisurely bath, a brief walk, or whatever activity is seen as relaxing, it can give a welcome respite from the feeling of being unable to cope. Other members of the family may be quite willing to take over for these brief periods when they see how helpful it can be.

Many couples find that they have disagreements which repeatedly emerge during premenstrual times. Often the discussion becomes heated to the point where productive problem-solving cannot take place. In such situations, often the best thing a couple can do is simply agree to stop the discussion with the agreement to return their attention to the issue at hand when moods are calmer, perhaps in the first half of the next cycle. It is important, however, that the issues raised premenstrually not be dropped entirely or dismissed as being unimportant. Rather, more useful problem-solving can be undertaken when both people can approach the issue more calmly.

Some couples have found the premenstrual time to be useful to them in a very positive way. They find that the increased feelings of sensitivity at this time can make them aware of disagreements or issues between them that they might not have otherwise been able to detect. They can then use this insight for understanding their relationship better and helping it to continue to grow as time goes on.

Hormonal Treatments

Much has been said and written about the role of hormones in causing premenstrual symptoms. Most scientists now feel that there are different chemical changes that cause premenstrual symptoms, but these changes are likely to involve chemicals in the brain rather than hormones produced by the ovaries. Specifically, no convincing evidence has turned up to say that PMS is caused by a simple deficiency of one hormone or another, such as progesterone.

Nevertheless, hormonal treatments have been used effectively as medications (not as replacements for a "deficiency"), and are often employed when the measures described so far are not sufficiently helpful. The two general types of hormone treatments that are used are those that 1) eliminate or suppress a woman's own hormone cycle, perhaps replacing it completely with hormones taken as medication, and 2) add to or supplement a woman's own hormones.

In the first group, those treatments that eliminate a person's own hormone production, are oral contraceptives (birth control pills), continuous use of medroxyprogesterone (a synthetic progesterone-like compound), hysterectomy with removal of both ovaries, estrogen implants with the periodic use of progesterone either in the form of regular progesterone or medroxyprogesterone, and finally recent experimental work with a hormone called GnRH agonist, which works at the brain level to shut down a woman's own menstrual cycle. We would like to say a little about each of these individually.

It has been known for many years that oral contraceptives will reduce premenstrual syndrome symptoms in general. However, some women with more severe premenstrual depression before going on the pill stand a greater chance of that depression worsening if they try the pills for contraception. About half of women who notice worsening depression on the pill will have that depression relieved by taking about 50 mg of vitamin B_6 daily. Perhaps because of the worsening of depression in some people and because of some other general concerns about the pill, it has been suggested that the birth control pill will always aggravate PMS symptoms. This is not the case, and the pill remains a useful form of treatment for some women. There is no evidence that being on the pill makes a woman more likely to get worse PMS symptoms after discontinuing it. In our own clinic, we suggest the birth control pill for those who have experienced no negative side effects from it in the past and for whom no other contraceptive method is as appropriate.

Medroxyprogesterone acetate (Provera), is the drug that has been used for many years to regulate episodes of irregular bleeding. Its actions are very similar to those of regular progesterone and it can be taken by mouth. For this reason it has been used by some clinicians to treat PMS, but apparently with mixed success. Although several studies show no effect of this compound on PMS, numerous clinicians have reported that some people do quite well on it while others find that their depression is aggravated by it. Our experience agrees with this and we recommend it only occasionally. We discourage the use of the injectable form of medroxyprogesterone acetate due to the fact that it will remain in the system for 3-4 months after each injection. If any negative side reactions take place it can take a long time for the drug to be eliminated from the body.

Removal of the ovaries certainly brings about some relief of PMS symptoms in some physicians' experience. However, there are no published reports documenting this, and most clinicians feel that this is rather drastic treatment for a disorder that can be quite effectively treated medically. Also, following removal of the ovaries, replacement hormones are necessary to maintain proper bone strength and proper lubrication capacity of the vagina as well as to eliminate hot flashes. These hormones will sometimes bring a return of some of the symptoms of PMS, although usually to a less severe degree.

In England, several physicians have used implanted pellets containing estradiol, an estrogen compound, to treat PMS. In order to prevent a precancerous overgrowth of the lining of the uterus (endometrial hyperplasia), they need to give progesterone or a progesterone-like compound for 10-14 days out of each month as well. This regimen essentially replaces a person's own hormone cycles with those provided by the medications and seems to treat PMS quite effectively. However, when the cyclic use of a progesterone-like compound is given as well, some of the PMS symptoms seem to return. This medication has not been proven safe for general use and is not available in this country.

Finally, recent work with gonadotrophin-releasing hormone (GnRH) agonist has demonstrated once more that if you shut down the function of the ovaries, premenstrual symptoms will disappear. However, this is very preliminary work and it is not available or recommended for general use as a treatment for PMS. There are significant problems that remain to be worked out with this treatment, especially the possibility of osteoporosis, or weakening of the bones, due to estrogen deprivation while on this treatment.

In general, although the treatments listed above are somewhat effective, they work by eliminating the menstrual cycle rather than adjusting or treating it in order to control symptoms. Our philosophy is that this is perhaps more meddlesome than hormone supplementation therapy as described below.

Dr. Katharina Dalton of England has been the most vocal proponent of progesterone supplementation therapy for treatment of PMS. There is now a growing experience in this country with this medication including the work done in our clinic. Although truly accurate studies have not been done to show that progesterone is more effective than a placebo, many clinics using progesterone find that the apparent effectiveness of the medication seems to last much longer than the 2-3 months one would expect a placebo to last. While awaiting further scientific studies to demonstrate its role, many clinics are continuing to use it in one of several forms.

Progesterone supplementation therapy is usually confined to the second half of the menstrual cycle, starting at or around the time of ovulation and continuing until approximately day 27 or 28 of the cycle, just before the anticipated menstrual flow would begin. It can be given in one of several forms: rectal or vaginal suppositories, a fluid used rectally as a "micro enema," drops placed under the tongue or injections.

A number of different types of suppositories are available, but some recent evidence suggests that the best absorption is obtained using polyethylene glycol (PEG) base suppositories. Although these are somewhat inconvenient and sometimes messy to use, most PMS sufferers find that they can become accustomed to using them either rectally or vaginally or alternating between these routes. We have found quite good results using between 200 mg and 400 mg per day divided into two doses with the PEG base suppositories. Our limited experience in seeing patients using higher doses indicates that they did not reach significantly higher blood levels with very large doses. Promising research is currently going on to investigate a way of delivering progesterone via nasal medication.

It is important to keep in mind when using these various hormonal measures to treat PMS symptoms that they are being used as medications to treat symptoms and not as the replacement for a known hormone deficiency. In this light, one might reach a point when other measures become more effective and hormone therapy is no longer required.

Other Medications

Aside from the hormonal and nutritional medications already mentioned, numerous other drugs have been used. We mentioned briefly that diuretics, or fluid pills, are widely used although they have no proven benefit. The only diuretic that has any evidence supporting its effectiveness in PMS is spironolactone. Used in amounts between 50 mg and 100 mg daily, some women find it effective. We generally have used this only when true weight gain has been documented by daily records, in order to avoid the possible hazards of dehydration from excess diuretic use.

Drugs that affect a person's emotional or psychological status, or psychoactive drugs, have also been used. These include many of the commonly employed anti-anxiety drugs and antidepressants. Although there are no controlled studies of these drugs in PMS, we have found them useful in several ways. First, drugs for anxiety can be used on an intermittent basis especially if a person's most severe symptoms are limited to only a few days before the onset of menstrual flow. This allows significant benefit with minimal chance for developing a physical addiction to the medications or a tolerance that would lead to the use of high doses. Some of these drugs do make a person feel a bit sleepy and therefore when symptoms last longer than just a few days, many women find that they feel more comfortable using progesterone than they do putting up with the sleepiness for a week or two at a time.

The last group of drugs in common use is the antidepressants. We have found it useful to use antidepressants primarily when there is some evidence of depression all month long which gets worse premenstrually. We sometimes then use antidepressants in combination with progesterone, a combination which seems to work better than either drug by itself. We employ this combination only with psychiatric consultation.

Counseling

Many women experiencing premenstrual changes find that over months and years of having symptoms, their lives and relationships have been gradually eroded or damaged. Even when symptoms are improved with appropriate medication, they still find that they have a significant amount of recuperating to do in an emotional sense. For this reason, many individuals and couples find it helpful to take advantage of the benefits of individual, family, or couples therapy in addition to some of the medication treatments for PMS.

Premenstrual symptoms can also happen along with other disorders such as anxiety disorders, panic disorders, continuous depression, and manic depressive illness. It is sometimes useful to combine both medical and psychological treatments for these problems with some of the treatments described above. It often works out best if the physician or other health care provider responsible for PMS care has a good working relationship with one or more people in the counseling fields.

Support Groups

Women suffering from PMS in many cities throughout the country have gathered together to form support groups. These groups meet on a fairly regular basis to share their experiences in attempting to cope with PMS symptoms, and to share hints on dietary adjustments, exercise programs, problem solving techniques in their relationships, and finding appropriate sources of medical care. Such groups can be a very valuable source of emotional and practical help in dealing with symptoms associated with PMS. They can also assist a woman in deciding when her symptoms are serious enough to require more comprehensive evaluation and treatment.

Several national groups maintain a roster of support groups and also of sources of medical care for PMS. These include the National PMS Society, 3514 University Drive, Durham, NC 27707; and PMS Action, P.O. Box 19669, Irvine, California 92713.

Medical Care for PMS

The essentials of evaluation, in our view, are 1) prospective daily ratings of symptoms, ideally by the person affected by PMS and by her partner or someone who is close to her, and 2) some assessment of personality, relationships, and general stresses and strains in life. When symptoms are not very severe, and/or when a physician knows the patient well, this can be effectively carried out in the primary care physician's office. When symptoms are more intense, or when more comprehensive evaluation seems appropriate, referral to a center with an established evaluation program may be helpful, with a plan to return to the primary care physician for followup care at an appropriate time.

Summary

There is now a growing recognition that premenstural changes are real, that definite (although poorly understood) chemical changes probably do account for many premenstrual symptoms and that medical diagnosis and therapy are therefore indicated. At the same time, most clinicians dealing with premenstrual syndrome and many women affected by it also recognize that there are many ingredients in the mix, many factors that affect how a person feels premenstrually. Until we understand a bit better the exact nature of the problem, it seems best to assess as best we can the various ingredients or contributing factors and apply treatments that seem most appropriate for each one.

Hormonal and other drug treatments are very helpful. They are most effective when used together with the diet and lifestyle changes previously mentioned. If life stresses can be reduced and unsolved problems worked out, it is sometimes possible to discontinue these medications and maintain symptom relief with the non-medication methods. Counseling or therapy is useful for many.

Finally, there is more hope now than ever before for women experiencing severe PMS. Many treatments are now available, and our understanding of the problem is growing as more and more research is done in this very important area of women's health care.

Sources of care for PMS associated with medical centers in North Carolina are

Duke Premenstrual Syndrome Clinic
Box 3308
Duke University Medical Center
Durham 27710
919/684-5322

Premenstrual Syndrome Clinic, Division of Reproductive Endocrinology
Department of Obstetrics and Gynecology
North Carolina Memorial Hospital
Chapel Hill 27514
919/966-5026

James L. Mathis, M.D.
Department of Psychiatry
East Carolina University School of Medicine
Greenville 27834
919/757-2660

Alive But Not Living

Eugene A. Stead, Jr., M.D.

Mac Mauney and I independently flagged the article in the February 8, 1985 issue of *JAMA* entitled "Just Alive, Or Living" for use in the *North Carolina Medical Journal*. I quote the paper in its entirety:*

"There are those, particularly in the medical profession, who would state that 'just alive or living' are the same conditions, but they are not. We who live in nursing homes (as I do at age 81) see all too vividly the difference between the two states of existence.

"I hasten to say that I am not a morbid person. I do not entertain an unhealthy death wish, nor do I advocate euthanasia. I still love living, even with all of its present restrictions, its many disappointments, and, too often, its painful times. The beauties of Nature, even seen through blurred vision, still delight me. I still thrill to a beautiful sunset and look on it as a wonderful harbinger of something good ahead and not just as an ending of another day.

"I treasure the good and interesting things in life and would like to feel I can enjoy them to the end, but the choice is not mine any more than it is the choice of the people I see about me to be bedfast or tied in a wheelchair. Some are no more than vegetables, but not from choice. Some have been lawyers, judges, teachers — and, yes, physicians. Their hearts beat and they breathe with or without the help of oxygen. So yes, they are alive, but one can hardly call it living. Of all of mankind's emotions, sometimes anger and sorrow seem to be the only ones left. Day after day and week after week these people just exist. They have become shells that house the spirit and nothing more. Time means nothing to them.

"Perhaps Nature has a better plan. I remember summers on the farm when I would find a cicada in its shell, clinging to the bark of a tree. Sometimes it would be there for a few days, but there would come a morning when I would find the shell split and the insect gone. The shell had finished its purpose for being.

"Medical science is a marvelous thing, and its forward strides are almost unbelievable. I would hope that research could go on and on, finding ways to help people have better and healthier lives. This, of course, particularly relates to prenatal through adult life, as long as there is still hope for a life that is meaningful to the person. I have a very deep interest in a large children's hospital and follow its reports of progress. If many of the things considered common practice today had been available at the time we elderly people were young, our whole lives could have been different.

"There was a time when pneumonia was called 'the old folks' friend.' When body functions had failed, pneumonia often gave the *coup de grace*. But today, antibiotics can bring these persons back from the very brink of death. But back to what? One can hardly call being fed, bathed, clothed, and changed and knowing nothing at all really living.

"I have been told that physicians take the Hippocratic Oath that describes the duties and obligations of a physician to maintain life. Isn't that carrying tradition rather far? I am sure you are not using the methods used by Hippocrates in 400 BC. If he could come back today, I wonder if he would not be horrified to see how patients who are really dead to all that means living are kept in a state of existence by the help of machines. Maybe the Oath needs some revising. It is hard to think of anything else that many centuries old that is still in use.

"We owe so much to science and to the physician's application of science. It has helped us travel in greater comfort over many of the rocky roads of life. Alleviation of pain is so greatly appreciated and certainly allows us to enjoy living in ways that would be impossible if every waking hour was just more time to endure pain. No patient can ever adequately express to his or her physician what real, kind help means to those who are ill.

"But there comes a time, a time when our bodies and too often our minds just wear out. Organ replacement for the elderly becomes a little like placing new parts in an old television. That part may work, but it isn't long before some other part wears out. At best you are only buying a little time for the patient — time for what? By the time we have reached our 80s and 90s, surely we have made whatever contribution to life that we are capable of, and I doubt that many of us could do it the second time around.

"Please! When all vital signs show the end is near, unless very drastic measures are taken, let us go. Prolonging a life for a person whose mind and body no longer function is an achievement for the physician, but do ask yourselves whether you are doing the patient any kindness.

"I just hope that I won't be alive any longer than I can live — but I will not be doing the choosing when that time comes."

Mauney, in his letter to me, says, "The simple, but eloquent, prose that this writer uses to make a statement about life and death values is so eloquent that I think it deserves reprinting in our *North Carolina Medical Journal*.

"Personally, I have espoused Lola Armstrong's viewpoint for many of my professional years. She simply has made me feel better about what I have tried to do professionally. The 'choice' is clearly the physician's and not a court of law. The responsibility

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* The author is Lola M. Armstrong of Lawrenceville, Illinois. Reprinted with permission from JAMA 1985; 253:789.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

of the decision mandates that that physician will have taken the time and made the effort to know his patient's life values and philosophic viewpoint, as well as his or her 'symptoms and signs'."

At the time these papers crossed my desk I was preparing a response to a paper by Elaine Brody entitled "Institutional Versus Home Health Care of the Elderly." My theme was that the time has come to recognize the dementia of partial brain death as the beginning of the dying process and in proper circumstances to make no attempt to prolong life by influenza vaccine, antipneumococcal vaccine, antibiotic, feeding and drinking beyond what the person can do for himself. I wrote as follows:

"It is easy to be a good citizen until one reaches the age where dependency overtakes us. We have not yet found an easy or graceful way for most of us to leave the stage on which we performed adequately as independent persons.

"The question is what to do. I know of no way to make dependency as attractive as independence. The devotion of all our resources to the care of the dependent elderly would not make old age as attractive as youth.

"We have to face a most difficult issue: what level of care do we want to give to what groups of persons? Professionals in aging have rarely faced this problem directly. They want more of everything and would have the surroundings and personal services equal to those of the independent population.

"We have accepted that comatose persons who have dead brains may be declared dead even though circulation and respiration can be maintained. Will we in time accept dementia as slow dying, and when it disconnects the patient from his surroundings will we make no attempt to prolong life? In a demented person, what is the purpose of the medical procedures, the administration of food and water, the use of antibiotics, the daily vitamins, the polypharmacy? It is not to help the patient enjoy life. Too much of the brain is dead. We care for the partly dead person because we have not developed an ethical or religious system that allows us comfortably to call it quits. We are afraid that we will become dehumanized if we don't postpone death. The care is for the living and not for the dying. We face the same issue with birth control and abortion. The egg, sperm, and embryo never complain. It is the feelings of the persons who live that are at stake.

"When I have cockroaches in my living quarters, candy in every nook and corner, a refrigerator filled with rancid food, and have stopped bathing, I won't care. My children will be appalled and want to instigate change. They are afraid I'll break my hip and die before I'm found. If I'm institutionalized, what is the minimal acceptable care that society can offer?

In the old days it was simpler. In 1930 Dean Wilburt Davison, a renowned pediatrician, came to the medically under-served Southeast. He was in great demand as a consultant who could work out a care plan for demented children who placed heavy demands on the family and community. The consultation had some aspects of a festive occasion. When Dean Davison got down to business, he requested everyone except members of the family to leave. He then determined who was going to contribute personal services or money for support of the child. He asked all other family members to leave. The final hard choices were then made by persons who had to implement them from their own resources.

"In our day the family is not dependent on their own resources. They have a variety of community, state and federal resources to cushion them. Insurance coverage, Medicare, Medicaid, state and community agencies dilute the feelings of personal responsibility. If we let patients finish the act of dying without intervention we must ask ourselves: are we letting demented persons die because we don't want to pay more taxes? Are our actions moving us to tolerate a new holocaust because there is no ethical basis for nonintervention?

"It is interesting that we have devised cultural and ethical systems that allow us to kill millions of healthy persons without feelings of guilt. We have a name for that system. We call it war. Until we have a philosophical and ethical system which accepts death as a part of life and acknowledge that the last part of living is the first phase of dying, we will make no progress. How will we develop an ethical base for new types of behavior? I assume that it will come about by forces tangential to problems we are discussing today.

"Two changes in our culture have occurred by a tangential approach. Knowledge that cancer is caused by exposure of our bodies to a variety of chemicals has changed much of our behavior. You no longer have to put out ash trays when doctors congregate in large groups. Workers in chemical plants are forcing management to adopt new methods of reducing exposures. Years ago no one thought that prevention of cancer would be possible and that prevention would produce major changes in our lives. Cancer is now recognized as the work of man on biological systems. It is no longer an act of God.

"Eventually a new generation will come to believe that there are limits to the amounts of money and services they are willing to expend for the dying section of the population. The concept of partial brain death and ways to deal with it will emerge. By one device or another a system of behavior compatible with this belief will evolve, and society will permit the partially dead to complete the act of dying in peace.

"Meanwhile we struggle with the economics of home and institutional care. I've no objection because we must fill in time while forces that we have not yet anticipated mold our attitudes."

Living is not simple but in our society dying may be even more difficult.

TOXIC ENCOUNTERS

Taljaribu Kila Dawa Isifal: Yohimbine Intoxication

Ronald B. Mack, M.D.

- *Yohimbine, a new street drug, comes from the bark of a tree grown in Africa. In overdose it is not pleasant.*

SURELY this is not an article on interplanetary hallucinogens or extraterrestrial aphrodesiacs. Nor is it a paper extolling the love-making enhancement of powdered rhinocerous horn, but it comes close. Yohimbine is a relatively new street drug whose origins are in Africa.

The Africa of my youth seemed to be a country of great mystery and intrigue; of European colonies, of wild animals and, of course, of Tarzan. Possibly my imagination was fueled by Edgar Rice Burroughs, Ernest Hemingway, Robert Ruark and the great movies like The Snows of Kilimanjaro, King Solomon's Mines, Stanley and Livingston, Bwana Devil, etc. Now the only thing about the country that is the same as I imagined it, is the shape — what with new countries with new names and new forms of government and famine and war and seemingly endless turmoil. But then again yohimbine comes from there. It was a gift we could have done without.

Yohimbine enjoys some reputation as an aphrodesiac and hallucinogen as advertised in pornographic magazines (my mother will not allow me to read them, so some of this material is hearsay) and also this drug is known to have stimulatory effects on the CNS. That's the good news. The bad news is that yohimbine is available by prescription and can be ordered in large quantities without prescription from mail order houses. It is available in some herb stores and can be brewed as a tea. I'm not sure why it has increased in popularity, but people who are "into drugs" seem to be constantly seeking new "highs" and "turn ons" and this one is being touted as a new "street" drug.

Yohimbine, believe it or not, is a drug that is found in the bark of yohimbe, which is an African tree. It is also listed in pharmacology texts as an *alpha-2 adrenoreceptor antagonist*. (You are joshing, aren't you, you want us to believe that African tree bark contains catecholamine inhibitors? The next thing you know you will have us believe that "sniffing" fire-extinguisher agent fumes can make us "high." Well actually, that is true, and may be the subject of a future anecdote.) Alpha receptors are present in the eye, blood vessels, genitourinary, and gastrointestinal tracts. The administration of alpha stimulating drugs such as norepinephrine or phenylpropanolamine or phenylephrine causes vasoconstriction, pupillary dilatation, a decrease in GI mobility and GI secretions, contraction of GI and GU sphincters and bladder contraction. So called "pure" alpha agonist poisoning could be predicted to cause hypertension and vagally mediated reflex bradycardia which could be life threatening. If you are ever faced with such an emergent situation, phentolamine (Regitine) is considered the antagonist of first choice. Alpha agonists can of course have powerful CNS effects such as tremor, seizures, panic reactions, sensory distortion, hallucinations and psychotic manifestations. If these latter clinical features are troublesome you could try diazepam (Valium) or haloperidol (Haldol) if the adrenergic antagonist fails.

Well, what about alpha-2 adrenoreceptor blockers, like yohimbine? These blockers (AKA antagonists) should produce, in overdose, miosis, postural hypotension, reflex tachycardia, angina (not common) and an increase in gastric acidity. The adrenergic blockers also have CNS effects, usually stimulation.

Alpha blocker poisoning is really not common. There are only a few types of these drugs around, e.g., phentolamine, phenoxybenzamine, prazosin, dibenamine, and of course, yohimbine. I mean really, pushers don't walk up to you on the street and say "Hey buddy, want to buy some phenoxybenzamine?" I have a cousin who tried to work his way through school (his ultimate ambition was to be a bartender at a rest camp for embattled secretaries of Department Chairmen) by selling Regitine as a street drug. Needless to say he failed and he is now confined to the Illinois State Home For The Criminally Foolish.

I suppose all of the above makes yohimbine's use as a drug of abuse really weird. The chemical known as yohimbine (AKA quebrachine, aphrodine, and corynine) is a *harmine* analog. Harmine and harmine-like chemicals have the potential to produce hallucinations. Harmine and harmatine are indole alkaloids found in several psychotropic plants, especially in the bark of certain South American vines. The alkaloids are hallucinogens and are rather powerful monamine oxidase inhibitors. Yohimbine (one street name is "Yo Yo") can produce an alpha adrenergic block of relatively short duration. Although CNS action does occur, it apparently is less than what occurs with ergot alkaloids. Although it has been recommended as a blood pressure lowering agent it can in fact *increase blood pres-*

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27104.

sure. Yohimbine can cause a local anesthetic action like cocaine as well as cause vasodilation of the skin and mucous membranes especially the sexual organs (please forgive me, I know this is a family magazine but I just couldn't help myself). It is currently being advertised as a smoking preparation whose ultimate purpose is "effortless seduction." (Land of Goshen, if one wants effortless seduction, one should make a visit to Madame CaCa's House of The Seven Moons on I-85.) This chemical can be ingested, smoked or imbibed as a tea.

Symptoms and signs of yohimbine overdose include weakness, hypertension, tachycardia and abdominal pain. Apparently massive overdose can produce generalized stimulation of the nervous system resulting in paralysis. It has been alleged that if this paralysis affects the intercostal muscles, the diaphragm, etc., then death can ensue simply because you stop breathing. Other adverse effects include irritability, tremors, antidiuresis and really a general picture of central excitation. Yohimbine enhances neural release of norepinephrine which may account for some of its sympathomimetic actions.

In a recently reported case of yohimbine overdose[1] as a result of drug abuse, the young victim experienced generalized weakness, paresthesias, loss of coordination and a dissociative state. This unhappiness was followed by chest pains, palpitations, tremors, severe headaches and dizziness. Upon examination at an emergency facility, she had hypertension, tachypnea, tachycardia, and temperature elevation. The patient was described as pale, tremulous and anxious. Her serum *norepinephrine* level was elevated. It is quite possible to identify yohimbine via high performance thin layer chromatography.

What should you do when confronted by such a patient, assuming you were able to make the diagnosis? (One solution is to call yourself on your pager and let someone else struggle with the case.) The management of yohimbine overdose can be very confusing. Although this drug is an alpha-adrenergic blocker and you would expect hypotension and reflex tachycardia as a result of overdose, we have seen that this drug can actually cause hypertension. It has been suggested, and quite appropriately in my opinion, that *clonidine* may be the drug of choice to reverse the adverse effects of yohimbine toxicity. Clonidine, you may recall, acts centrally by stimulating alpha-adrenergic receptors and causing a reduction in sympathetic tone as well as peripherally blocking alpha-adrenergic receptors and reducing vascular activity.

One of the aspects of seeing movies about Africa and reading stories about the "dark continent" is that we tend to forget that it was our first introduction to Swahili — the language of East Africa. The natives consistently referred to the employers as Bwana (sir, master, mister, boss, etc.). The other word you consistently heard at times of great excitement was Umgawa, Bwana!! (Remember?) Exhaustive research in the Swahili literature reveals no such word as umgawa. It probably was made up by Hollywood script writers. The main title of this treatise is in Swahili of course, and means "we have tried every medicine that you gave us but they are all useless." Now, doesn't that sound familiar — many the problems of the health care provider, no matter where in the world, they are universal. Jambo!!

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Mail to **N.C. Medical Group Associates,** P.O. Box 13121, Greensboro 27405.

References

1. Linden CH, Rumack BH, et al. Yohimbine: A new street drug. Abstracts from the Proceedings of the AAPCC, AACT, ABMT, CAPCC Annual Scientific Meeting, San Diego, CA, October, 1984.

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Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly

Information for Patients: Headache may occur during initial therapy with SORBITRATE Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent

Carcinogenesis, Mutagenesis, Impairment of Fertitity: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended The extent to which development of tolerance should modify the dosage program has not been defined *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg), Sustained Action Tablets (40 mg).

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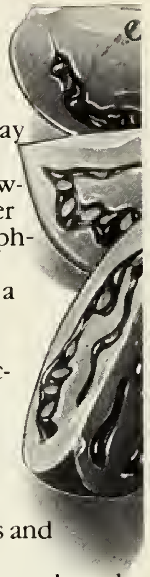
A defense against cancer can be cooked up in your kitchen.



There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.

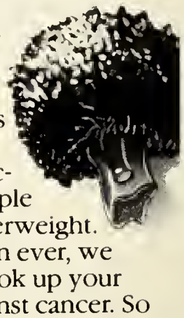
Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash, and tomatoes, citrus fruits and brussels sprouts.

Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

Be moderate in consumption of alcohol also.



A good rule of thumb is cut down on fat and don't be fat. Weight reduction may lower cancer risk. Our 12-year study of nearly a million Americans uncovered high cancer risks particularly among people 40% or more overweight.

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No one faces
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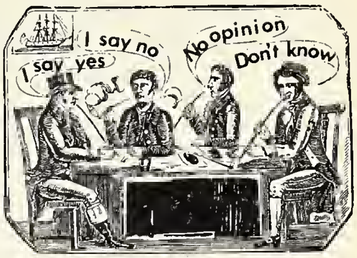
PHYSICIANS' FORUM

Preadmission Certification: Does It Constitute the Practice of Medicine?



Eugene W. Linfors, M.D., editor

The question for April is: **In your personal opinion, does the refusal of precertification for admission to the hospital by insurance companies constitute the practice of medicine? Should they be held liable for malpractice?**

From Dr. J. Trig Brown, an internist in Durham.

It is well known that physicians are the major cause of escalating health care costs. To think that precertification for admission by insurance companies constitutes the practice of medicine is absurd; these benevolent companies are simply overseeing that area that physicians have failed so blatantly to police. The operating premise is that physicians use hospitals inappropriately for their own personal gains. Consider the following scenario.

MD: I'm calling for precertification for admission for my patient, Mr. N. Need.

Insurance Company (IC): What is the reason for admission?

MD: This elderly man has bad chronic obstructive pulmonary disease and is not doing well.

IC: Is not doing well . . . Doctor, what do you mean?

MD: Well, you see, his wife who performed his chest physiotherapy has just died, his fuel subsidy has been stopped, and he's now got an upper respiratory infection. I'm concerned that this may decompensate him.

IC: Nothing you have said allows me to authorize a hospitalization. What objective criteria do you have?

MD: On physical exam his respiratory rate is 30, he is somewhat febrile, and his sputum is green, thick, and tenacious.

IC: According to my guidelines a respiratory rate of 30 does not qualify for admission, what is his temperature?

MD: Orally it is 38^2; however, he has trouble keeping the thermometer in his mouth because of his dyspnea.

IC: 38^2 is not high enough, Doctor, you know we have our guidelines. Do you have blood gases?

MD: Why yes, his pO_2 is 58 and his pCO_2 is 52.

IC: Are those values acute onset, sudden onset, recent onset, or recently or newly discovered?

MD: What?

IC: *Acute* is within 6 hours, *sudden* is within 24 hours, *recent* is within one week, and *recently or newly discovered* was not present at the previous examination.

MD: Oh, I see. Well his gases at admission last fall were slightly worse, but we never repeated them because clinically he was doing so well until last week.

IC: So, these gases are not recently or newly discovered. Doctor, we are only trying to help you. What would you plan to do with the patient in the hospital?

MD: Mr. Need has always done well with twice daily percussion and postural drainage, adjustment of his theophylline, and antibiotics.

IC: Good, we're on to something. Will the theophylline and antibiotics be given intravenously?

MD: Well, no, actually we can get therapeutic levels orally at a cheaper cost and with less discomfort to the patient.

IC: Will he be on the intensive care unit?

MD: No, you see, Mr. Need has a living will and in it he stipulates that he not be on an intensive care unit.

IC: Well, Doctor, you have a problem. Although none of the objective information documents a severity of illness appropriate for admission, you do come close. But, on the other hand, the intensity of services planned do not substantiate the need for admission. I am sorry but I have no other choice but to disallow this request for hospitalization.

MD: I hear what you are saying but I still don't know how to adequately treat Mr. Need as an outpatient.

IC: I'm sorry Doctor, we don't practice medicine, that's your problem.

Physicians practice medicine and are liable for malpractice. The trend toward precertification for admission rekindles memories of Alexander Haig's infamous misstatement "I'm in charge here." It is clear the person in charge should be liable for malpractice and insurance companies are not in charge . . . or are they?

From Dr. Charles O. Boyette, a family practitioner from Belhaven.

In my opinion, preadmission certification requirements by insurance companies or any other designated body does indeed constitute the practice of medicine. Admission or denial of admission has a direct effect on how that patient is treated and managed, and in turn will significantly affect recovery from illness or continuing disability.

No physician is perfect and the practice of medicine is complicated and variable. It seems today that everyone — government, insurance carriers, and so many others — wishes to become involved and dictate how the sick are to be treated and under what circumstances. With these handicaps the ultimate loser will invariably be the patient. The attending physician and the patient will forever remain the most competent authorities as to the need for hospitalization.

As to liability in preadmission certification, there is no question but that insurance companies should be held liable in cases of denial for admission which results in disability or more severe consequences such as death. The prevention of a small number of admissions will never atone for the potential hazards and losses should the advice of the attending physician be ignored.

Doctors are being placed in an untenable and liable position and this should not be. Insurance companies and government are not practitioners of medicine. They should simply state what they can finance and what they can not in contracts with their clients and leave the practice of medicine to those who are professionals in patient care.

From Dr. William W. Fore, an endocrinologist in Greenville.

Most physicians consider the physician-patient contract for payment to be the responsibility of the patient and not his/her insurance company. Many physicians request payment of fees and then refund to the patient when the health insurance carrier pays. A denial in the precertification process is a declaration before the fact that the insurance carrier will not pay for the admission because their consultants believe the patient can be cared for as an outpatient. The patient's admission occurs from a decision that is made by the physician, the patient, and the hospital. It is not the practice of medicine for an insurance company to deny payment before the fact.

One industry in North Carolina obtained a 55% decrease in hospital utilization without having a patient denied by the precertification process. Precertification works and will be necessary unless all physicians in North Carolina work to voluntarily decrease hospital utilization.

From Clark C. Havighurst, a professor of law in Durham.

No. An insurer's refusal in advance to pay for a hospitalization advised by a physician does not constitute the practice of medicine. The insurer is not deciding on medical treatment but is only giving effect to a contractual limitation on its obligation to pay for marginally beneficial medical treatment. The patient is still free to decide, with his physician's advice, to accept hospitalization (at his own expense). The medical decision is thus entirely distinct from the insurer's decision on payment.

No. An insurer cannot be sued for medical malpractice. The insured's rights against the insurer are governed in the first instance by the insurance policy, and the proper claim in any lawsuit would be for breach of contract. Some states allow insureds to sue insurers for bad faith in interpreting policy language and refusing to pay valid claims, and punitive damages are occasionally awarded in such cases. Unless a court were thoroughly confused (they often are), the test for bad faith would not be anything like the test that would apply if a physician failed to provide the treatment in question. Moreover, because the insurer did not itself prevent treatment from being rendered, the damages would probably not be measured by the injury suffered.

From Dr. Andrew W. Walker, a plastic surgeon in Charlotte.

No, I do not believe the refusal of precertification for admission to the hospital by the insurance companies constitutes the practice of medicine. The physician has a responsibility to recommend to his patient whether he or she should be admitted to the hospital. The insurance company decides whether the hospital and the physician should be paid or not. This in no way should interfere with what the doctor feels is right for his patient. The patient and insurance company have entered into an agreement without the doctor's input. The patient must, therefore, bear the burden of the bill if the insurance company elects not to pay it. The physician should remind the patient that this is the case. A second opinion could be gotten from a second physician if the patient so wishes. I believe if the insurance company has refused too many patients for hospitalization they may be sued by their clients and the courts would then have to decide if it was a failure to fulfill a contract. Whether this would constitute malpractice or not I do not know.

• EDITOR'S NOTE: Two of our respondents argue that refusal of precertification for hospitalization does constitute the practice of medicine while three see it as a separate contractual issue between the insurance company and the patient. Informal discussions with some of my colleagues have mirrored this difference of opinion. I don't think we've heard the end of this discussion.

Five opinions, even when stated as well as our respondents have, do not constitute a true survey. I try to anticipate several sides to an argument in asking for opinions. I am grateful to those who do respond. Some, for various reasons, choose not to respond in print. If, after reading the Forum, you see a particular point of view underrepresented, please write it down and send it to me.

We also invite opinions on the question for the next Forum. **"What would you advise our Medical Society to do and say regarding ecology and pollution?"** Please send your response by April 22 to: Eugene W. Linfors, M.D., Box 3381 Duke University Medical Center, Durham 27710.

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WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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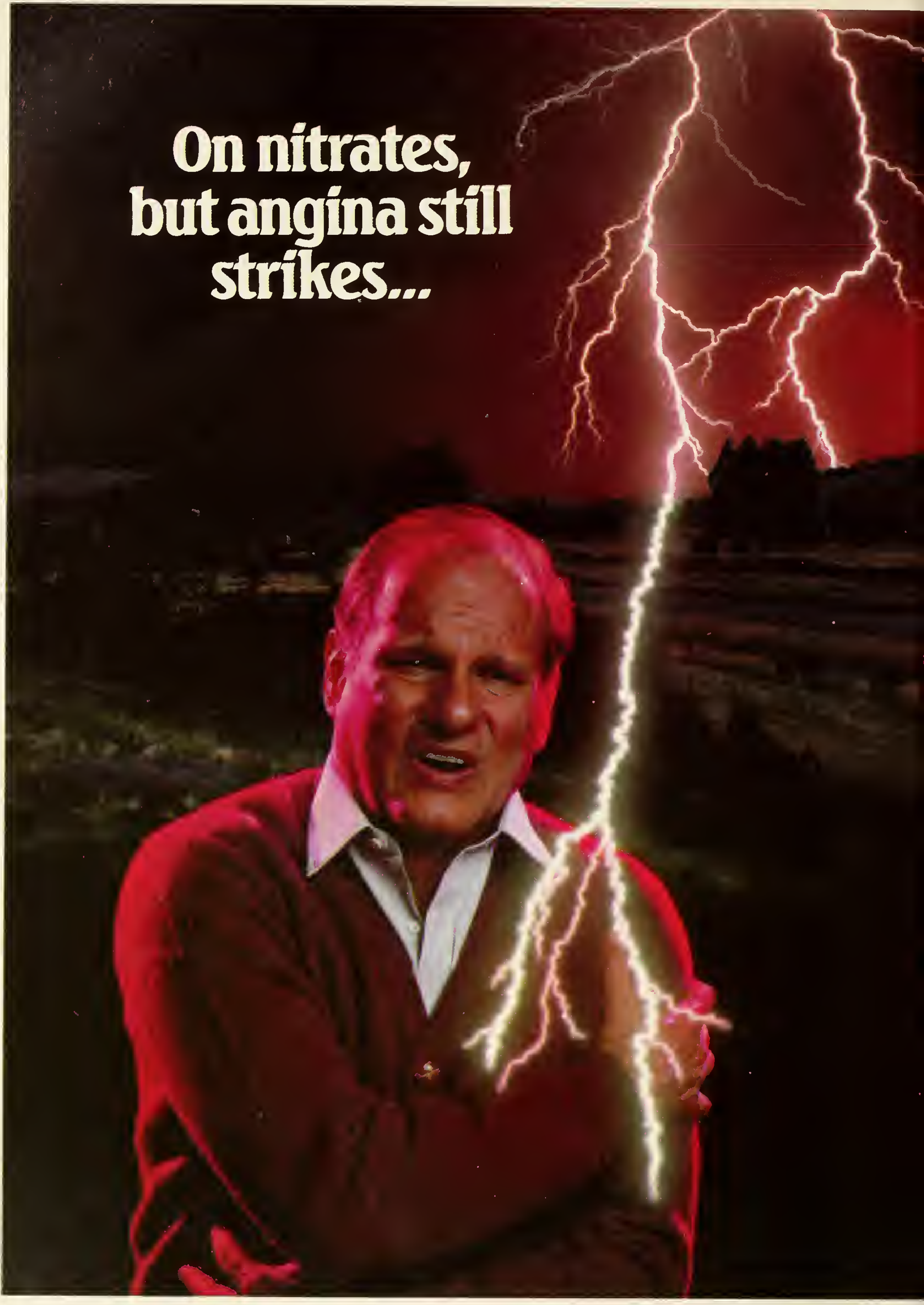
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Second, Isoptin spares patients the beta-blocker side effects that may compromise the quality of life.

With Isoptin, fatigue, bradycardia and mental depression are rare. Unlike beta blockers, Isoptin can safely be given to patients with asthma, COPD, diabetes or peripheral vascular disease. Serious adverse reactions with Isoptin are rare at recommended doses; the single most common side effect is constipation (6.3%).

Cardiovascular contraindications to the use of Isoptin are similar to those of beta blockers: severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no artificial pacemaker is present) and second- or third-degree AV block.

So, the next time a nitrate is not enough, add Isoptin . . . for more comprehensive antianginal protection without side effects which may cramp an active life style.

ISOPTIN. Added antianginal protection without beta-blocker side effects.

Please see brief summary on following page.

ISOPTIN® TABLETS

(verapamil HCl/Knoll)

80 mg and 120 mg

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets. July 1982 2068

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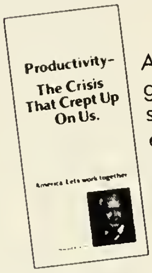

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Coalition on Sexually Transmitted Diseases

Marguerite K. Tracy

EDITOR'S NOTE: *A coalition* to combat sexually transmitted diseases has been formed by the United Way of Charlotte. They hope that the Coordinating Council of Specialty Societies will submit a report which will be presented to the House of Delegates at the annual meeting of the North Carolina Medical Society. The exact wording of such a report has not been finalized, but the gist can be summarized by three resolutions. These resolutions were formulated because the members of the Coalition believe that there is a need for private patients to have an alternative to public health clinics and access to a fee-for-service physician, knowledgeable in both the diagnosing and treating of sexually transmitted diseases. The Coalition believes that there is a large pool of physicians in North Carolina capable of treating sexually transmitted diseases, but there is no readily identifiable mechanism whereby private patients can be referred to fee-for-service physicians. The three resolutions follow:*

RESOLVED, that the North Carolina Medical Society commit itself to a public service project for the people of North Carolina by organizing a statewide network of physicians who would be willing to accept referral of private *''Fee For Service'' patients for the evaluation and treatment of sexually transmitted diseases; and BE IT FURTHER*

RESOLVED, that the North Carolina Medical Society, in cooperation with AHEC and other educational resources, would provide continued medical education in sexually transmitted diseases for those physicians who join in this statewide network of private physicians; and BE IT FURTHER

RESOLVED, that the North Carolina Medical Society, after creating the network, commit itself to a public awareness program, and facilitate the general public's accessibility to this statewide physicians network.

The following article contains the background information that led to the formation of the Coalition.

The problem

Back in the 1940s, we assumed that antibiotics would forever control the terrible diseases such as tuberculosis and syphilis, which were at that time common and pandemic. For the next 20 years health care personnel became very complacent as they saw the ''wonder drugs'' cure these ills and others.

During this period of complacency, a new pandemic of sexually transmitted diseases has developed. In spite of wonder drugs, we are back to the drawing board. Some of the newly identified sexually transmitted diseases have probably existed for centuries. Improved laboratory and epidemiologic investigations have defined the extent of the epidemic and the life-threatening consequences of these diseases. The "coming of age" of the children of the post-World War II baby boom has made the control of sexually transmitted diseases more urgent. There are simply more people and more sexual activity.

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* *Further information about the Coalition can be obtained from Pete Auerbach at 704/375-0222. Mrs. Marguerite Tracy of Charlotte, chairman of the Coalition, is immediate past president of the North Carolina Medical Society Auxiliary. The current members of the Coalition are Melinda Wharton, M.D., Durham; Don C. Chaplin, M.D., Burlington; Albert M. Collier, M.D., Chapel Hill; Robert Greenup, Fort Bragg; Dr. Raphael DiNapoli, Raleigh; Raymond S. Combs, Camp Lejeune; Robert Williams, M.D., Seymour Johnson AFB; James Fowler, Jr., Raleigh; Frankie Barnes, Raleigh; June Stallings, Raleigh; George Shackelford, Raleigh; Martha Jacob, Jacksonville; Lottie Daw, New Bern; Pam Kohl, Raleigh; Gwin Hughes, Raleigh; Lorey White, Jr., Louisburg; Frank McFall, Atlanta, GA; Margie Rose, Raleigh; Family Life Council of NC, Raleigh; Kate Garner, Ph.D., Greensboro; Hugh Tilson, M.D., Research Triangle Park; Roy Parker, Jr., Fayetteville; Charles Russell, Wilson; Spurgeon Cameron, Raleigh; Fred Sparling, M.D., Chapel Hill; Sandra Mayben, Fayetteville; Harry A. Gallis, M.D., Durham; Nick Engel, Winston-Salem; Brenda S. Coble, R.N., Greensboro; Midgie Rawley, Charlotte; Dean Garver, Shelby; Madeline Hunter, Winston-Salem; Lauren Kirkpatrick, Raleigh; David Citron, M.D., Charlotte; Kathryn M. Frye, Charlotte; A. D. Sawyer, Chapel Hill; Pete Auerbach, Charlotte.*

We now recognize not only two sexually transmitted diseases but 26, including herpes, hepatitis, and AIDS. And yet only two diseases are required to be reported: gonorrhea and syphilis.

The National Institute of Allergies and Infectious Diseases Study Group reported that in 1980, the incidence and occurrence of sexually transmitted diseases were as follows:

- 7 million new or recurrent episodes of genital herpes
- 3 million infections due to chlamydia
- 3 million trichomoniasis cases
- 2 million cases of gonorrhea
- 0.5 million cases of venereal warts, and
- 0.1 million new cases of syphilis

These millions of cases in turn led to:

- 1 million cases of pelvic inflammatory disease
- 0.3 million damaged infants
- 0.2 million women rendered infertile, and
- *$2.5 billion* in direct and indirect costs.

They also cause death, physical deformity, mental retardation, ectopic pregnancy, infant pneumonia, and possibly five different cancers.

These numbers are misleading because they represent only a fraction of actual cases. Venereologists estimate that these numbers may represent only 1/10 of all cases. Most of the reported cases are hospital or clinic based. A study performed by the American Social Health Association in 1963 and 1971 revealed that no more than 12% of sexually transmitted diseases treated by U.S. physicians were reported. A 1980 *American Journal of Public Health* article reported that approximately 60% of gonorrhea cases seen by private physicians in Denver, Colorado, were not reported.

Many persons who are carrying some sexually transmitted diseases have no symptoms. Consequently, there is much unrecognized spread of diseases like chlamydia, gonorrhea, and especially herpes.

Let's look at some specific diseases and their influence.

Gonorrhea. Although more than 1 million cases have been reported in the U.S. annually for the past four years, it is believed there are over 2 million actual cases per year. The highest rates of infection are found among young adults, ages 20 to 24 years, and teenagers, ages 15 to 19. An estimated one of every 30 teens in the 15 to 19 age group will contract gonorrhea each year. Women continue to be the primary victims of gonorrhea, accounting for 90% of all complications.

Chlamydia. Results of studies indicate chlamydia has overtaken gonorrhea as the number one sexually transmitted disease. Since chlamydia is difficult to recognize by the female patient and difficult to culture, and because reporting is not mandatory, documentation of prevalence is difficult. But, again, women are the major victims of the disease, which is responsible for at least 20% of all pelvic inflammatory disease, 11,000 cases of sterility, and 3600 ectopic pregnancies.

Syphilis. According to the Centers for Disease Control in Atlanta, reports show that within the last two years there has been a surge in the number of cases of syphilis, to approximately 100,000 new cases each year.

Herpes. This was first identified in 100 A.D. It now affects 15 to 20 million Americans representing 500,000 new cases annually. Women and children are the primary victims. Because of ineffective control and an average annual recurrence rate of 5%, this disease is expected to rise rapidly. There is no cure for herpes.

Acquired Immuno-Deficiency Syndrome (AIDS). More than 40% of those infected are dead within a year; there is no cure. Since 1981, AIDS has struck 788 people in the U.S. and 57 abroad, killing 295. What a waste to us individually and collectively!!

North Carolina had the first venereal disease control program in the U.S. in the early 1930s. This was a program paid for by Z. Smith Reynolds Foundation, which is still interested and involved.

Some startling facts are:

- North Carolina has the 7th highest rate of gonorrhea in the nation.
- North Carolina ranks tenth in the nation in the amount of syphilis. Charlotte has a reported infectious syphilis rate nearly seven times the national average.
- In 1983, 425 children between the ages of 10 and 14 years were reported to have been infected with gonorrhea in the past year. A total of 1123 young people between the ages of 15 and 19 years were infected in North Carolina in 1983.
- Currently, there are 2 million cases of gonorrhea annually identified, costing about $1 billion annually!
- Reported cases of syphilis have doubled annually since 1961.
- Over 80 cases of AIDS have been reported and verified in North Carolina.
- The most startling fact: *one of every four individuals in the work place is infected by a sexually transmitted disease* (this is a report from the Public Health Disease Center in Atlanta).

With all this, we do not calculate the cost in dollars suffered by industry because of related illness, absenteeism and poor performance on the job.

Our Solution

We do know what we should do to set up a control program. The Coalition on Sexually Transmitted Diseases is composed not only of health care personnel, such as doctors, public health nurses, and members of the State Infectious Disease Programs, but also includes industry, the military, social services, the North Carolina Medical Society, the North Carolina Medical Society Auxiliary, the state PTA, youth advocacy personnel, the Department of Public Education and others.

The Coalition has drafted five goals and related strategies for reducing this pandemic. Our first objective is *to insure that every student in North Carolina receives accurate, timely education about sexually transmitted diseases as part of a comprehensive health education curriculum.* Because of a policy statement sent to and passed by the legislators in June 1984, 16 additional health coordinators were added. We now have 32 health education coordinators.

The second objective is *to improve the public's understanding of sexual transmitted diseases, and their social and economic impacts, as well as its knowledge of preventive techniques and treatment options.* The Coalition purposes to accomplish this through a public awareness program, using appropriate levels of information. Much of present material is out-dated, obsolete, and inconclusive.

The third objective is aimed at *developing training programs for health professionals to accord them current information.* This can be accomplished by providing the health education and clinical experience in schools for health professionals.

The fourth objective will *encourage every employer (industry, military, commerce and government) to provide health services at the work place to include sexually transmitted disease education, testing and health care.*

The fifth objective deals with *improving and increasing access to services in the treatment of any sexually transmitted disease.* This will include evaluation of hours of operations of clinics, to be more compatible with patient needs and to more involve qualified physicians to provide answers, care and treatment.

The Coalition is composed of quality people with a caring concern for the community and it is their hope to provide a better understanding and an increased awareness of this major health problem.

This is but a portion of the program of work, but is a good synopsis of the direction of the Coalition.

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NORTH CAROLINA MEDICINE TODAY

Aging in its many aspects

It is estimated that 25 million people (11% of the population) are over age 65, and represent the fastest-growing segment of the population by far. It is further estimated that this group currently spends approximately 75 billion dollars annually for personal health care, and accounts for some 55% of all federal health dollars.[1] For these reasons alone, studies concerned with various aspects of aging are of vital importance to the entire nation. Much major research in this complex area is being conducted in North Carolina, at its several medical centers and universities, often under grants from the National Institute on Aging.

Studies cover a wide range

Recent studies have reported on the physiological dynamics of aging as related to circulatory diseases and circulatory risk factors at advanced ages (over 85) as compared to findings in a study population with a mean age of over 70 years.[2] Another study, stemming from the comprehensive Duke First Longitudinal Study, evaluated Wechsler Memory Scale scores as related to distance from death and the potential use of the WMS as a predictor of survival in both normal and demented elderly populations,[3] while yet another compared young and old adults in the spontaneous use of context to learn and recall information.[4]

Dealing with America's fourth leading killer disease

Researchers at Duke University Center for the Study of Aging are focusing on the study of Alzheimer's disease, a type of primary neuronal degeneration that is the most common form of dementia. Estimates vary but indicate that as many as 4 million older Americans[1] are afflicted with this illness, which has been labeled "the disease of the century."[5] Concurrent with its medical research on Alzheimer's disease, the Duke University Center is providing innovative support mechanisms for afflicted families and other caretakers. A hotline provides callers with telephone consultations, introductions to others close by in similar circumstances, and practical medical, legal and psychological information. The Center has also aided in the establishment of 19 local support groups statewide, and regularly makes available information on Alzheimer's disease to health providers, nursing homes and hospitals, and others responsible for programs and services directed toward the victims of this killer disease.[6]

References: **1.** Hoson MK, Slock NL, Mooney RP: *W Va Med J 79* 98-102, May 1983 **2.** Monton KG, Woodbury MA *J Gerontol 38* 406-413, Apr 1983. **3.** Siegler IC, McCorty SM, Logue PE: *J Gerontol 37*:176-181, Feb 1982 **4.** Hess TM, Higgins JN: *J Gerontol 38* 65-71, Jan 1983. **5.** Roach M: *NY Times Mag*, Jan 16, 1983, p 22 **6.** Gwyther L: *NC Med J 44*:434-436, Jul 1983

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*Feighner JP, *et al. Psychopharmacology* 61:217-225, Mar 22, 1979.

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Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

> ***Usage in Pregnancy:*** **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: *Double strength (DS) Tablets,* white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets,* blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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Annual Meeting Program

131st Annual Meeting of the North Carolina Medical Society,
May 1-5, Pinehurst Hotel, Pinehurst, NC.

Wednesday, May 1

9:00 a.m. Resident Physician Section, *Crystal Room*
1:00 p.m. Resident Physician Lunch, *Main Dining Room, West End*
2:00 p.m. Medical Mutual Insurance Company Risk Management Seminar, *Cardinal Ballroom*
Committee on Blue Shield, *Pine Room*
2:15 p.m. Resident Physician Section, *Crystal Room*
6:30 p.m. Resident Physician Reception, *West Porch*
7:00 p.m. Resident Physician Dinner, *Crystal Room*

Thursday, May 2

7:00 a.m. AMA Delegation Breakfast, *Crystal Room*
8:00 a.m. MEDPAC Board, *Pine Room*
8:30 a.m. Section on Public Health and Education, *Azalea Bar*
10:00 a.m. House of Delegates, *Cardinal Ballroom*
11:45 a.m. Lunch Buffet, *Main Dining Room*
12:00 p.m. MEDPAC Lunch, *West Lawn*
2:00 p.m. Reference Committee I, *Cardinal Ballroom*
Reference Committee II, *Azalea Bar*
Reference Committee III, *Board Room*
Section on Otolaryngology and Maxillofacial Surgery, *Crystal Room*
Section on Urology, *Pine Room*
6:00 p.m. ECU School of Medicine Alumni Reception, *West Porch*
Medical College of Virginia Alumni Reception, *Lower Lobby*
Exhibitors' Reception, *West Lawn*

Friday, May 3

7:00 a.m. NCMS Officials Breakfast Caucus, *Main Dining Room*
8:30 a.m. Conjoint Session, *Cardinal Ballroom*
N.C. Academy of Family Practice, *Azalea Bar*
N.C. Pediatric Society Executive Committee, *Room 129*
9:00 a.m. First General Session, *Cardinal Ballroom*
Section on General Surgery and Section on Plastic and Reconstructive Surgery, *Resort Club*
Obstetrics/Gynecology Liaison Committee, *Mid Pines Resort*
9:30 a.m. N.C. Commission for Health Services, *Pine Room*
10:00 a.m. N.C. Pediatric Society Liaison Committee, *Crystal Room*
11:00 a.m. N.C. Orthopaedic Association Executive Committee, *Magnolia Room*
11:45 a.m. Lunch Buffet, *Main Dining Room*
12:00 p.m. N.C. Academy of Family Physicians Lunch, *Main Dining Room, West End*
Section on Ophthalmology Lunch, *Main Dining Room, East End*
N.C. Orthopaedic Association Executive Committee Lunch, *Magnolia Room*
12:30 p.m. N.C. Pediatric Society Liaison Committee Lunch, *Crystal Room*
1:00 p.m. N.C. Orthopaedic Association, *Pine Room*
2:00 p.m. Section on Pediatrics and Section on Allergy and Clinical Immunology, *Cardinal Ballroom*
Section on Ophthalmology, *Crystal Room*
Section on Orthopaedics, *Pine Room*
Section on Family Practice, *Azalea Bar*
Section on Emergency Medicine, *Magnolia Room*
Medical Student Section, *Room 129*
N.C. Society of Internal Medicine Executive Committee, *Merion Villa*
Section on Obstetrics and Gynecology, *Mid Pines Resort*
Section on Plastic and Reconstructive Surgery Business Meeting, *Mid Pines Resort*
5:00 p.m. Section on Allergy and Clinical Immunology Business Meeting, *Board Room*
N.C. Society of Internal Medicine Reception, *Merion Villa*
5:30 p.m. Duke University Medical School Alumni Reception, *Front Porch West End*
UNC School of Medicine Alumni Reception, *West Porch*
6:00 p.m. Bowman Gray School of Medicine Alumni Reception, *Azalea Bar Porch*
6:30 p.m. President's Reception, *Lower Lobby*
7:30 p.m. President's Dinner and Dance, *Cardinal Ballroom*

Saturday, May 4

7:00 a.m. NCMS Officials Breakfast Caucus, *Main Dining Room*

8:00 a.m. Section on Dermatology, *Crystal Room*
Section on Anesthesiology, *Pine Room*
Section on Neurology and Section on Psychiatry, *Azalea Bar*
8:30 a.m. Second General Session/Section on Internal Medicine, *Cardinal Ballroom*
9:00 a.m. Section on Radiology and Section on Nuclear Medicine, *Magnolia Room*
Section on Pathology, *Resort Club*
10:00 a.m. Committee on Mediation, *Board Room*
11:30 a.m. Section on Psychiatry Business Meeting, *Azalea Bar*
Section on Neurology Business Meeting, *Room 129*
11:45 a.m. Lunch Buffet, *Main Dining Room*
12:00 p.m. Section on Dermatology Lunch, *West Porch*
New Hanover-Pender Lunch and Caucus, *Board Room*
12:30 p.m. Pitt County Caucus, *Room* 129
1:00 p.m. Mecklenburg County Caucus, *Azalea Bar*
Forsyth County Caucus, *Magnolia Room*
2:00 p.m. House of Delegates, *Cardinal Ballroom*
Section on Neurological Surgery, *Crystal Room*

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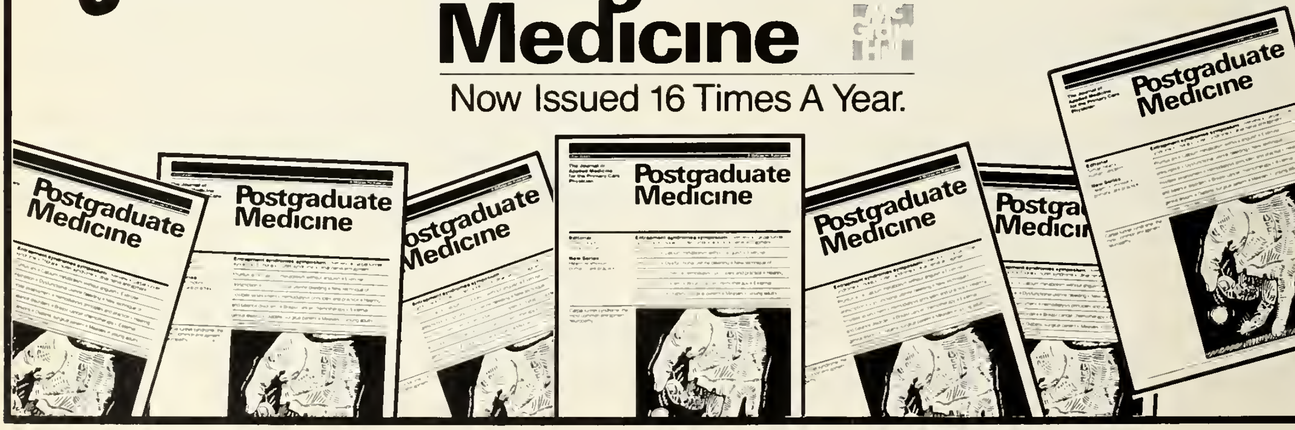

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Brief Summary of Prescribing Information

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See section under **Special Notes on Administration and HOW SUPPLIED.**
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DESCRIPTION

Norlestrin Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE

Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0.05 per 100 woman-years, in clinical trials with Norlestrin 2.5/50 involving 96,388 cycles, there was a pregnancy rate of 0.22 per 100 woman-years.

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS

1. Thrombophlebitis or thromboembolic disorders.
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral vascular or coronary artery disease.
4. Known or suspected carcinoma of the breast.
5. Known or suspected estrogen-dependent neoplasia.
6. Undiagnosed abnormal genital bleeding.
7. Known or suspected pregnancy (See WARNING No. 5).
8. Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved.

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage.

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions.* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

3. *Carcinoma.* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors.* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring.* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease.* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects.* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure.* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache.* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. *Bleeding Irregularities.* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-Feeding.* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS

1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.
2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.
7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.
10. Certain endocrine and liver function tests and blood components may be affected.

(a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives: thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension; gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma, breast changes, change in weight, change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature, intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

After several months on treatment, bleeding may be reduced to a point of virtual absence. reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED

Norlestrin $\boxed{21}$ 1/50 is available in compacts each containing 21 tablets. Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin $\boxed{21}$ 2.5/50 is available in compacts each containing 21 tablets. Each tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin $\boxed{Fe}$ 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin $\boxed{FE}$ 2.5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets. Each pink tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin $\boxed{28}$ 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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LEARNING WITHOUT WORDS

The Diagnosis of Viral Pneumonitis in a Compromised Host: Is An Aggressive Approach Warranted?

Dale Sargent, M.D., Elizabeth Mease, M.D., and James F. Howard, Jr., M.D.

- *Transbronchial biopsy was necessary to find the cause of illness in a woman immunocompromised by treatment for her myasthenia gravis.*

WHEN evaluating a pulmonary infiltrate in an immunocompromised host, one is faced with an endless array of possible causes for these infiltrates, both infectious and non-infectious. Empiric therapy directed at even a few of the most likely pathogens involves regimens with serious potential for toxicity. An aggressive diagnostic approach in these patients will often allow more specific and less toxic therapy resulting in an overall decrease in morbidity. The following case illustrates this principle.

A 60-year-old woman had myasthenia gravis for 18 months. Her treatment consisted of cholinesterase inhibitors; intermittent plasma exchange; a prior thymectomy; azathioprine, 50 mg three times daily; and prednisone, 70 mg every other day. She presented with three weeks of fever; night sweats; anorexia; weight loss; and painful, migrating, red skin papules. For two weeks, she had a non-productive cough without hemoptysis or chest pain.

Physical exam revealed a cushingoid, tachypneic woman with a temperature of 37.8°C. There were red, non-fluctuant, 1-2 cm tender papules on the right arm, buttocks, and left anterior tibial region. There were findings of consolidation over the left upper lobe of the lung and +2 pretibial edema. She had 4/5 muscular strength. The white blood cell count was 8,800/mm^3 with a normal differential. A chest radiograph showed an alveolar infiltrate in the left upper lobe (figure 1).

Multiple blood, urine, and sputum cultures were negative for bacterial pathogens, fungi, and mycobacteria. A skin biopsy of the papules showed acute and chronic inflammation with no pathogens seen on histologic sections or culture.

Although the patient seemed to have an infectious illness, the differential diagnosis was broad. Because of the length of her illness, we felt routine bacterial pathogens were unlikely. More likely were the opportunistic pathogens such as pneumocystis (although it rarely causes focal infiltrates), fungi (including blastomyces, aspergilli, and cryptococci), tuberculosis, legionella, or nocardia. The viral pneumonias seemed unlikely, again because of the focality of the infiltrate. Clearly it was impossible to initiate therapy for all of these organisms, so a diagnostic procedure was performed.

In our hands, transbronchoscopic lung biopsy is diagnostic in over 75 percent of compromised hosts with pulmonary infiltrates. The morbidity and mortality of this procedure are also very low. Therefore, on Day 2, a transbronchial biopsy was done. The biopsy showed a polymorphonuclear infiltrate, interspersed with lymphocytes and plasma cells. Intranuclear inclusions, consistent with cytomegalovirus (CMV), were present (figure 2). Stains and cultures for bacteria, legionella, mycobacteria, and fungi were negative.

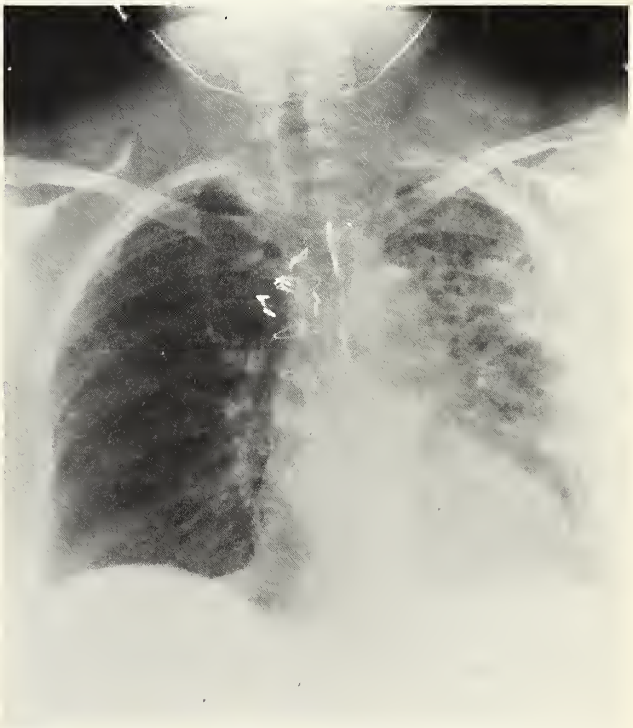

Figure 1. *A chest radiograph on hospital Day 10 showing the left upper lobe alveolar infiltrate.*

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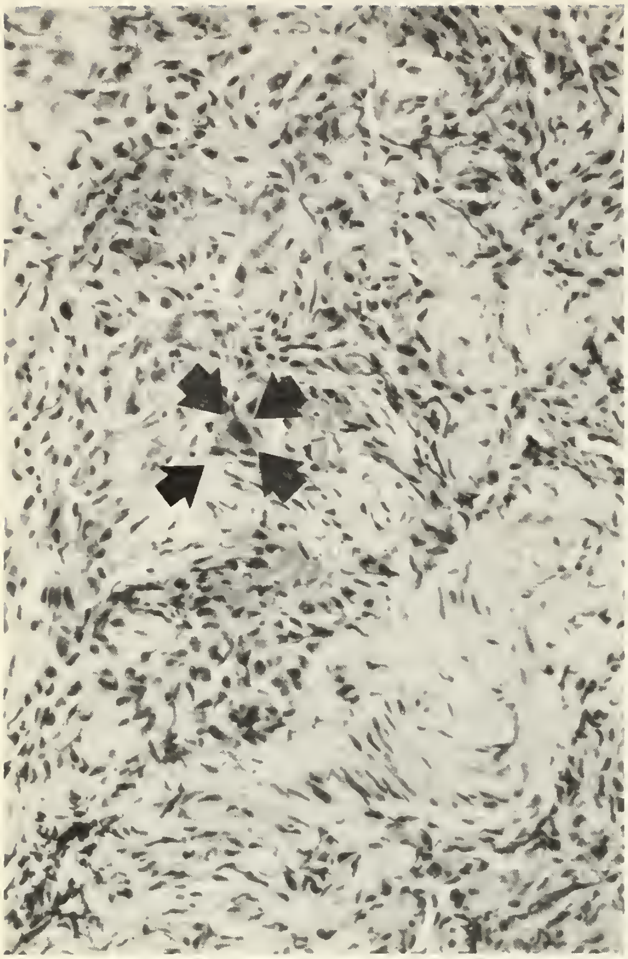

Figure 2. *A section from the transbronchial biopsy showing an intranuclear inclusion (arrows) consistent with CMV infection (hematoxylin and eosin, original magnification × 250).*

Despite the finding of CMV on the initial biopsy, we were unwilling to ascribe the illness to CMV alone. CMV has been described to cause focal infiltrates only rarely[1, 2] and CMV infection frequently occurs in the company of other pathogens[1, 3] (table 1). Therefore, we began Amphotericin B, Isoniazid, and Rifampin; stopped her azathioprine; and decreased her prednisone to 40 mg every other day. She continued to do poorly, with progression of her pulmonary infiltrates and continued fevers. Vancomycin was added on Day 6 and Trimethoprim/Sulfamethoxazole, on Day 10.

Because we were still worried that a significant pathogen was present and had not been diagnosed, we repeated the transbronchial biopsy on Day 11. The findings were similar to the previous biopsy, including the presence of intranuclear inclusions. Cultures of the specimen grew CMV but no other pathogens.

With this additional information we felt comfortable with the diagnosis of CMV pneumonia. All antimicrobial agents were stopped and her subsequent course was marked by gradual return of her temperature to normal and clearing of her infiltrate. Complement fixation titers to antibody to CMV were 1:256 both "acutely" and after recovery. She was discharged on Day 23 and remains well nineteen months later, taking only prednisone as an immunosuppressant.

Table 1
Pathogens Frequently Associated with CMV in the Lung

Pneumocystis Carinii
Herpes Simplex
Candida and Other Fungi
Gram Negative Bacilli

The diagnosis of CMV pneumonia was established by culture and pathologic examination of lung tissue. Although lobar CMV pneumonia is exceedingly rare, exhaustive investigation did not reveal other agents. Furthermore, our patient received inadequate therapy for fungal, mycobacterial, or pneumocystis pneumonia and did not begin to improve until all antimicrobials were stopped. The failure of CMV titres to rise does not exclude CMV disease, since the initial titres were drawn three weeks into the illness. Also, CMV titres may fail to rise in compromised patients with the most severe CMV disease.[1] The nodular skin lesions have been described as a manifestation of CMV disease and may represent cutaneous CMV infection.[4]

Outside of the transplant and acquired immunodeficiency literature, there are scant reports of CMV pneumonia.[1, 3-7] Both our patient and those reported by Dowling[5] were receiving cytotoxic therapy in addition to corticosteroids, suggesting an additive effect between these classes of drugs with respect to CMV disease.

Confirmation of the diagnosis of CMV pneumonia allowed us to stop several toxic antimicrobial agents. The importance of tapering or stopping her immunosuppressive therapy was emphasized and, we believe, led to this patient's recovery. In immunocompromised patients with pulmonary infiltrates, an aggressive diagnostic approach is indicated. If routine examination and culture of clinical specimens are not revealing, we believe either transbronchial or open lung biopsy is indicated, depending on the level of expertise available at a particular institution. Viral cultures should be obtained on biopsy specimens, even if the clinical picture does not seem to indicate viral infection. The isolation of CMV as the pathogen from a lung biopsy may allow the patient to be treated without potentially toxic antimicrobials even though specific therapy for CMV is not presently available.

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Transdermal Nitroglycerin

Lisa Hutchinson, Pharm.D.

IN 1982, three nitroglycerin products utilizing transdermal drug delivery systems entered the U.S. marketplace. These products were conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease pending final approval after clinical trials were completed. Until this time, the cutaneous application of nitroglycerin ointment was the only method available (except high dose oral isosorbide dinitrate) which avoided a high degree of inactivation in the liver. The ointment, although used successfully in the treatment of angina pectoris and congestive heart failure, had several limitations. It was inconvenient for many patients to have to apply an ointment several times daily, especially when it had to be covered with an occlusive dressing. The amount of drug absorbed varies with the area of skin over which it is spread, the ointment thickness, and the intrinsic properties of the skin at the application site.[1] The ointment is rather messy and not very practical for active patients. The innovation of the transdermal patches was intended to overcome these problems.

The purpose of this article is to review the pharmacology, pharmacokinetics, efficacy and use of the three transdermal nitroglycerin products currently available in the United States.

Pharmacological Properties

Angina pectoris occurs when there is an imbalance between oxygen supply and demand to the myocardium.[2, 3] The determinants of myocardial oxygen consumption are: 1) tension development during myocardial systole, 2) the contractile state of the heart and 3) the heart rate.[2] Symptoms of ischemia occur when the demand for oxygen by the myocardium cannot be met by the coronary blood flow.[2, 3] This is usually the result of coronary atherosclerosis which causes blockage of the coronary arteries, decreasing the blood supply to the myocardium.[2, 3] The area of the myocardium supplied by the blocked arteries becomes ischemic as the difference between supply and demand increases.[2, 3] This is usually accompanied by angina pain.[2]

Nitrates relieve angina pain by improving the balance between myocardial oxygen demand and supply.[2, 3] All nitrates act by causing smooth muscle relaxation which produces dilatation of arteries and veins.[2, 3] Although the exact mechanism of nitrate action at the cellular level is not completely understood, it has been proposed that nitroglycerin acts by combining with sulfhydryl groups on nitrate receptors in vascular smooth muscle.[4] Ignarro et al also suggest that vasodilation results when cellular cyclic GMP is increased by nitrate induced S-nitrosothiol production.[5] Dilatation of the venous system results in pooling of the blood in the peripheral veins, leading to a reduction in right heart blood return, cardiac filling (preload) and decreased tension on the walls of the heart.[2, 3] The lowering of systemic vascular resistance when the arterioles dilate produces a decrease in pressure against which the left ventricle must pump (afterload).[2, 3] Decreased mechanical activity, therefore, lowers myocardial oxygen requirements and metabolism.[2, 3]

Nitroglycerin's effect on the coronary arteries is less well understood. It has been shown to dilate normal and diseased coronary arteries and to increase blood flow to coronary collateral vessels.[6-8] During ischemia, nitroglycerin increases flow to the subendocardium, re-establishing the normal 1:1 relationship of endocardial and epicardial blood flow, thus increasing blood flow to ischemic zones of myocardium.[9]

In summary, nitroglycerin may relieve ischemia by decreasing myocardial oxygen demands and left ventricular diastolic pressure; by reversing coronary vasospasms; by decreasing coronary arteriolar resistance; and by improving regional blood flow. For a more in-depth discussion of the pharmacologic properties of nitroglycerin the reader is referred elsewhere.[3-9]

Clinical Trials

Numerous studies have been done to evaluate the utility and therapeutic efficacy of nitroglycerin patches.[10-17] The data documenting the antianginal effects of nitroglycerin patches and the comparative magnitudes and duration of this activity differ between studies.

Thompson studied eight patients in a double-blind crossover study comparing Nitro-Disc to placebo.[10] All patients were men, ages 38-70, with class II or III angina, coronary heart disease documented by coronary angiography or previous documented myocardial infarction, and characteristic ST-T segment changes during exercise; they were receiving no other medications. The patients were titrated over a 10 day period to receive the appropriate dose of nitroglycerin. This was done by starting with a 16 mg patch and increasing by one patch per day until persistent headache occurred or other side effects precluded further increase. The daily dose was then adjusted to that insufficient to produce side effects. All patients underwent treadmill exercise tests according to the Bruce protocol. The test involved four stages: a baseline exercise test on day 1, exercise tests 2 and 26 hours after receiving a placebo or nitroglycerin patch on days 12 and 13, exercise tests 2 and 26 hours after receiving the opposite treatment on days 15 and 16 and a follow-up exercise test on day 19 to establish baseline stability. They concluded that the Nitro-Disc increased the mean exercise capacity by 30% ($p < 0.05$) and that 26 hours after application the mean exercise duration was still prolonged by 25% ($p < 0.05$).

Reichek et al studied fourteen subjects (13 men and 1 woman) aged 50-70 with typical angina using a randomized double-blind placebo evaluation.[11] Coronary artery disease was documented by coronary angiography, exercise thallium or exercise echocardiographic studies. Eleven subjects received beta-blockers and five received calcium antagonists at a fixed dose throughout the study. Exercise testing was done on a Godart bicycle using the protocol of the National Institutes of Health. Seven subjects received a titrated low dose protocol, which is the smallest dose that would lower the cuff systolic pressure by 10 mm Hg or increase the heart rate at least 10 beats per minute in less than 2 hours. All received a baseline exercise test, then exercise tests after 4, 8 and 24 hours for 4 days during which they received either nitroglycerin patch or placebo. The effect of each subject's usual dose of sublingual nitroglycerin as a positive control was assessed on day 5. They concluded that there was no enhancement of exercise tolerance at 4, 8 or 24 hours after administration of the patch. A high dose protocol was then initiated using a maximal tolerated dose, defined as the dose that decreased systolic pressure to 90 mm Hg in normotensive, sitting patients or the largest dose that did not produce intolerable headaches. Improved exercise tolerance was seen at 4 and 8 hours, but was not seen at 24 hours. Even at maximal doses they found the effect on exercise tolerance to be surprisingly small. They suggest that nitroglycerin patches do not offer 24-hour coverage and would not recommend their antianginal effects to last for more than 8 hours.

The short- and long-term effects of various Nitro-Dur formulations on performance and hemodynamics were studied by Hollenberg.[12] A treadmill exercise test according to the Bruce protocol was used during this single-blind, dose-titrated study of 15 men with stable angina with positive treadmill exercise tests. After a control exercise test, each subject was tested at 4 and 7 hours with each of three different doses of Nitro-Dur (5 cm^2, 10 cm^2 and then either a 15 cm^2 or 20 cm^2 patch). After these short-term tests, long-term tests were begun. These tests were conducted on the first day of the study, both 2 weeks and 4 weeks after daily therapy was started, and 1 week after the application of a placebo patch. Results were that Nitro-Dur improved exercise tolerance by 31% ($p < 0.0001$) and the time required for 1 mm ST segment depression increased by 33% ($p < 0.0001$) in the short-term tests at all dosage levels. The long-term tests showed that the effects of Nitro-Dur on blood pressure became attenuated at 2 and 4 weeks, but cardiac responsiveness was preserved. They suggest drug tolerance or a neural-hormonal compensatory response to prolonged nitrates as the mechanism.

Georgopoulous et al studied the effects of the nitroglycerin patch in a randomized double-blind cross-over study.[13] A 25 mg nitroglycerin patch or a placebo patch was applied to 13 male patients, aged 32-63, with chronic, stable angina for 2 weeks and then the opposite treatment was applied for another 2 weeks. Exercise tolerance according to the Bruce protocol was performed at baseline and every week. Severity and duration of anginal pain evoked by exercise was recorded, and the intensity of the symptoms was graded on a four-point scale. ST-segment depression was measured according to Goldman. They found that transdermal nitroglycerin reduced the daily frequency of anginal attacks by 67%, the daily consumption of nitrates by 63% and exercise induced ST-segment depression by 50%. The anti-anginal effect was found to be more pronounced in the second week of treatment.

In a randomized double-blind, double cross-over trial of four one-week periods, Crean et al studied the effects of 25 mg of nitroglycerin in a 10 cm^2 patch versus placebo in 10 patients with stable angina and significant coronary disease.[14] Efficacy was assessed weekly by anginal diaries, exercise testing and 96 hours of ambulatory ST-segment recordings. They found that the nitroglycerin patch did not significantly reduce the number of anginal attacks per week, the consumption of sublingual nitroglycerin, the time to ST-segment depression, or the time to angina from that of the placebo patch. They concluded that no significant differences could be detected in objective or subjective signs of ischemia in patients treated with transdermal nitroglycerin or placebo.

There have been numerous investigations of the efficacy of nitroglycerin patches in the treatment of chronic stable angina. These studies differ significantly in their criteria for entry and efficacy, as well as in the use of concomitant medications and in the doses of nitroglycerin patch form supplied. The studies also use very small patient populations, therefore making the statistical significance of their conclusions difficult to interpret. It would be advantageous to develop a standard protocol in order to evaluate the efficacy of the patches. Studies that have the most effective design are double-blind, double cross-over, randomized placebo-controlled studies that try to maximize the amount of nitroglycerin applied. Until more standard protocols with larger patient populations are used, it will be virtually impossible to interpret these studies appropriately.

Pharmacokinetics

Transdermal drug delivery allows the drug to be absorbed from the skin into the capillaries under the skin and into the general circulation. This avoids the variable absorption sometimes associated with oral therapy and maintains a relatively constant drug level in the blood.[18] Transdermal drug delivery results in release of nitroglycerin at a rate that mimics a constant intravenous infusion.[19]

Although it is possible to measure plasma concentrations of nitroglycerin, there is no real correlation between plasma concentrations and pharmacological effects.[20, 21] Differences in storage and collection techniques, type of assay, sample site, route of administration, as well as intraindividual variability will result in variable serum levels.[20, 21] Counter-regulatory mechanisms and development of tolerance can complicate the relationship between the plasma concentration of nitroglycerin and its effects.[20, 21] It is also suggested that the pharmacological effects of nitroglycerin could be related to blood vessel wall concentration rather than plasma concentration.[22] Therefore, it is unwise to try to apply pharmacokinetic data obtained with different formulations or routes of administration to predictions on

Table 1
Comparison of Pharmacokinetic Parameters[26, 31]

Delivery System	Onset	$(C_{plasma})_{ss}$ pg/ml* per unit	per cm^2	Rate of absorption thru skin in vitro μg/cm^2/hr
Ointment 2% 4″ x 4″	30-60 min.	151.3±24.5	15.1±2.4	20.45
Transdermal				
Transderm-Nitro 5	30 min.	130.6±21.7	13.1±2.2	14.55
Transderm-Nitro 10	30 min.	209.8±22.8	10.5±1.1	—
Nitro-Dur 20	30 min.	201.4±60.7	10.1±3.0	16.67<12 hr and 10.50>12 hr
Nitro-Disc 16	30 min.	280.6±18.7	17.5±1.2	20.45

* Concentration in the plasma at steady state expressed in pg/ml.

pharmacological effects, efficacy and duration of activity.[20, 21]

Nitro-Dur (Key Pharmaceuticals) consist of a 2% w/w nitroglycerin in a polymer-gel matrix as its inner layer. The nitroglycerin is in equilibrium between a liquid phase and that absorbed on suspended lactose crystals.[23] Transderm-Nitro (Ciba Pharmaceuticals) is a reservoir system. Nitroglycerin is absorbed on lactose in a silicone medical fluid with silicone dioxide added to increase viscosity. This is enclosed by an ethylene-vinyl acetate copolymer membrane that is permeable to nitroglycerin. The nitroglycerin seeks out an area of lower concentration and passes out of the reservoir through the permeable membrane into the skin.[24] Nitro-Disc (Searle Pharmaceuticals) is a reservoir system which contains microsealed nitroglycerin evenly dispersed in a solid silicone polymer. The nitroglycerin moves from the polymer into a liquid pocket and then it is available to the skin.[25]

Relative skin permeability of nitroglycerin as delivered by transdermal patches was studied by Chien.[26] Table 1 summarizes the steady-state plasma profiles of the patches and expresses them in terms of area of skin treated. Nitro-Disc demonstrated greater bioavailability. Chien also studied the skin permeation of nitroglycerin and found both Nitro-Disc and Transderm-Nitro to have constant delivery over a 30-hour period. Nitro-Dur, however, showed a biphasic pattern with a rate change after 12 hours from 16.67 μg/cm^2/hr in the initial 12-hour period to 10.56 μg/cm^2/hr in the remaining period. Nitro-Disc's permeation is 25% greater than Transderm-Nitro at 18.15 μg/cm^2/hr and 14.55 μg/cm^2/hr, respectively. Both are higher than Nitro-Dur with an average of 13.62 μg/cm^2/hr. It was also found that the smaller size Nitro-Disc (8 cm^2) compensated for its higher rate of skin permeation making it interchangeable with Transderm-Nitro (10 cm^2) and Nitro-Dur (10 cm^2) in delivering equivalent amounts of nitroglycerin over 24 hours. A comparison of the pharmacokinetic parameters of the patches and ointment is given in table 1.

Administration, Dosage and Adverse Effects

In the past, the terminology used to describe the various patches has been a source of confusion. The FDA now requires that all manufacturers label the patches numerically by the amount of nitroglycerin delivered over 24 hours. Transderm-Nitro products have always been labeled in this manner, but Nitro-Disc products have just recently met this labeling requirement. Previously Nitro-Disc was labeled according to the total nitroglycerin content (MG). Nitro-Dur products are still labeled numerically according to the size of the patch (cm^2), but will meet the new labeling requirements in the near future. Table 2 compares the patches for size, nitroglycerin content, delivery and cost.

Dosing guidelines for all products are empiric, with relief of angina, the reduction of the number of sublingual

Table 2
Comparison of Nitroglycerin Patches[31, 32]

Product		Size (cm^2)	Content (mg)	Delivery in 24 hrs (mg)	Cost per unit†
Transderm-Nitro	2.5	5	12.5	2.5	$0.92
	5	10	25	5	0.96
	10	20	50	10	1.06
	15	30	75	15	1.16
Nitro-Dur	5	5	26	2.5	0.84
	10	10	51	5	0.88
	15	15	77	7.5	0.90
	20	20	104	10	0.93
	30*	30	154	15	—
Nitro-Disc	5	8	16	5	0.90
	10	16	32	10	0.96

* Not currently marketed in the U.S.
† Cost as average wholesale price as published in the *Redbook* 1984.

tablets taken or the development of side effects as end points.[3] Questions on equivalency between different nitrate dosage forms can only be established by controlled clinical trials. One author suggests that 0.5 inches of nitroglycerin 2% ointment applied over 20 cm^2 every 8 hours will produce approximately equivalent plasma levels with a once-daily dose of Nitro-Dur 20, Transderm-Nitro 10 or Nitro-Disc 10.[27] At this time it is not recommended that the patches be physically cut in order to individualize dosing, since the effect this has on drug delivery is not yet known. When nitroglycerin is discontinued, it should be tapered slowly over 4-6 weeks to prevent potential withdrawal reactions.[28]

The patches should be applied to hairless areas of the body, preferably the chest or upper arm. They should not be applied to extremities below the elbow or knees, to skin folds, scar tissue, burned or irritated areas. The site of patch application should be rotated daily to avoid irritation of the skin.

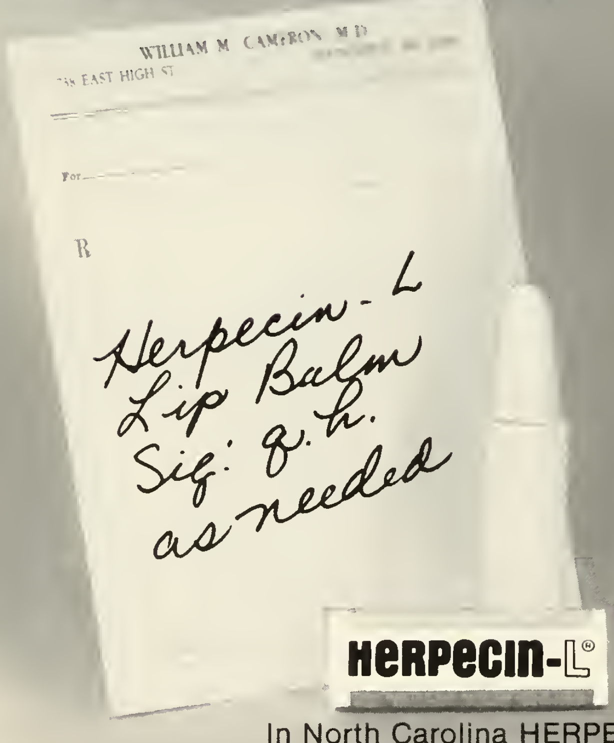
Adverse reactions to the patches are reported to be infrequent. Besides the typical nitroglycerin side effects of headache, low blood pressure, tachycardia, fainting, flushing, dizziness, nausea and vomiting, several dermatologic reactions have been reported.[29] These consisted of contact dermatitis, transient reddening of the skin surrounding the margin of the patch, and one case of a cutaneous burn-like reaction with atrophic changes and scarring possibly caused by the patch.

Conclusion

Transdermal delivery of nitroglycerin holds promise. It is convenient and may provide a means of achieving a sustained nitrate effect. However, at the present time, the data are inconclusive and controversial regarding the twenty-four hour efficacy of the nitroglycerin patches. More carefully controlled studies are required before final conclusions can be made. Clinicians should therefore be cautious when assuming adequate nitroglycerin effects for twenty-four hours in a patient with persistent angina.

References available from the NCMJ editorial office.

Dx: recurrent herpes labialis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In North Carolina HERPECIN-L is available at all *Crown, Eckerd, Kerr, Mutual Drug, Revco Drug Stores* and other select pharmacies.

Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

April 15-June 7
Postgraduate Course in Medical Sonics
Place: Winston-Salem
Credit: 35 hours Category 1 AMA per week
Info: James F. Martin, M.D., Center for Medical Ultrasound, Bowman Gray School of Medicine, Winston-Salem 27103. 919/748-4505

April 17
The Back — From Thoracic to Sacral
Place: Sanford
Credit: 2 hours Category 1 AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

April 24
Current Concepts in Otolaryngology for the Primary Care Physician
Place: Chapel Hill
Fee: $50
Credit: 6.5 hours Category I AMA, AAFP
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

April 25-27
New Expanded Advanced Cardiac Life Support Provider Course
Place: Asheville
Credit: 24 hours Category 1 AMA and ACEP and AAFP
Fee: $300
Info: Daniel L. Dolan, M.D., MAHEC, 501 Biltmore Avenue, Asheville 28801-4686. 704/258-0881

April 27
Rehabilitation of the Cancer Patient
Place: Chapel Hill
Info: Deitra Lowdermilk: 919/966-5390

May 1
The Pregnant Therapist
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-3571

May 3-4
House Officer Selection
Place: Chapel Hill
Fee: $325
Credit: 12 hours Category I AMA
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

May 17-18
Neurosurgery Laser Workshop
Place: Chapel Hill
Fee: $700
Credit: 15 hours Category I AMA; AANS-CNS
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

May 22
Antibiotics — The New Ones
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

May 23
Sexually Transmitted Diseases
Place: Chapel Hill
Fee: $20
Credit: 5 hours Category I AMA
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

May 24-25
Diagnosis and Treatment of Pediatric Hypersensitivity Diseases of the Lung and Gut
Place: Durham
Fee: $80
Info: Alexander Spock, M.D., Box 2994 DUMC, Durham 27710.

June 10-12
Surgery for Coronary Artery Disease
Place: Durham
Info: Robert H. Jones, M.D., Box 2986 DUMC, Durham 27710.

June 13-15
Advanced Clinical Ultrasound
Place: Winston-Salem
Fee: $400
Credit: 16 hours Category I AMA
Info: James F. Martin, M.D., Box 229, Bowman Gray, Winston-Salem 27103. 919/748-4505

OUT OF STATE

April 18-20
Radiology Review
Place: Hilton Head Island, SC
Fee: $350
Credit: 15 hours Category I AMA
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

April 19-21
Seventh Annual Conference on Emergency Medicine for the Primary Care Physician
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-27
Twentieth Annual Pediatric Springfest
Place: Williamsburg, VA
Fee: $235
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-28
Annual Meeting, Virginia Society of Otolaryngology-Head and Neck Surgery
Place: Irvington, VA
Info: Donna Strawderman, 4205 Dover Road, Richmond, VA 23221. 804/353-2721

May 3-5
Fifth Annual Clinical Concerns in Primary Care
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

May 10-12

Fifth Annual Radiation Oncology Course
Place: Williamsburg, VA
Fee: $275
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

May 25-27

Gynecologic Urology and Pelvic Surgery
Place: Hot Springs, VA
Fee: $250
Info: Eileen Hardigan, Box 538 MCV Station, Richmond, VA 23298. 804/786-0693

June 6-8

Rehabilitation of the Brain-Injured Adult and Child
Place: Williamsburg, VA
Fee: $275
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

June 12-15

Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Fee: $350
Credit: 15.5 hours Category 1 AMA, AAFP, NCMS
Info: Division of Dermatology, Box 3135 DUMC, Durham 27710. 919/684-2504

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BUNCOMBE

Charles Robert Shields (P), One Rotary Drive, Asheville 28803

BURKE

Lawrence Steven Wilson (U), Valdese Doctors' Clinic, P.O. Box 700, Valdese 28690

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Andrew Henderson Wells (Student), 1715 Elizabeth Ave., Winston-Salem 27103
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Jonathan Glen Dewald (IM), 1700 S. Tarboro St., Wilson 27893

Daniel Peter Michalak (OBG), 1700 S. Tarboro St., Wilson 27893

Letters to the Editor

A Fitting Handle

To the Editor:

I enjoyed and appreciated your editorial, "How the Handle Fit in 1960" in the December 1984 issue of the NCMJ (45:766-7). Your observations and philosophy are equally applicable in 1985. In the field of psychosomatic illnesses you write, "the physician is likely to attribute the symptoms to the area of his own greatest interest." How astute!

I was amused by your using the word "spangle." It's a rare word that could be used more often than it is.

Michael F. Keleher, M.D.
18 Maywood Road
Asheville 28801

EMT Study Guide

To the Editor:

As providers of training for basic emergency medical technicians (EMTs) who wish to become certified at the intermediate level (EMT-Is), we are concerned about the knowledge EMTs possess when they enroll in our training programs. The reason for our concern is that people tend to forget things they learn as time passes, particularly if they do not have opportunities to apply their knowledge. Since our training programs are offered to EMTs in rural areas, we must assume that this factor is operating to a greater extent than in urban areas. Therefore, we have developed a *Study Guide* to help EMTs review material presented in their basic courses and a pretest to provide feedback on the effectiveness of their review.

The primary objective of the review process is to help EMTs prepare themselves to profit from the instruction in the EMT-I Course. To this end, our *Study Guide* was developed by a committee of physicians and nurses with experience in providing emergency medical care, and it is keyed to the text recommended by the North Carolina Office of Emergency Medical Services for basic training programs. This committee also wrote the pretest, the results of which are made available to local review boards appointed by the hospital sponsoring the training program as they consider applicants for the program. We have monitored the performance of EMTs on the pretest and are happy to report that factors such as education, being a paid EMT, or length of service as an EMT have not influenced pretest scores to the extent that potentially successful applicants have been denied training.

While we cannot prove that the *Study Guide* is the cause of the applicants' high level of performance on the pretest, we believe that the *Study Guide* helps them structure their review of material they learned during their basic training programs and, perhaps more importantly, helps them focus on material that is the foundation of intermediate training. We also believe that the pretest increases the applicant's motivation beyond the level that would be achieved in its absence. Finally, based on the performance of EMTs trained in our programs on the state certification examination, we believe that our process helps us identify EMTs who can be expected to complete our training programs successfully and obtain certification.

We hope to publish a more complete report of our experiences, including supporting data, in the near future. In the meantime, we will be happy to share our experiences and data with interested parties. We also welcome any suggestions for improving the process we presently use.

Sandra S. Landis, RN/MICN
Theodore W. Whitley, PhD
E. Jackson Allison, Jr., MD/MPH
Department of Emergency Medicine
East Carolina University School of Medicine
Greenville 27834

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Jerrold Seckler, M.D.
Urologist

❝Because of the system we have, we're able to handle more patients, more efficiently, every day. My staff can access the information they need—when they need it—on each patient. That's a great help in appointment scheduling, preparing patient routing sheets and answering account inquiries. I can call up complete patient profiles or very specific data.❞

Anthony Daddono, M.D., S.C.
Allergist

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Cecil W. Hart, M.D., S.C.
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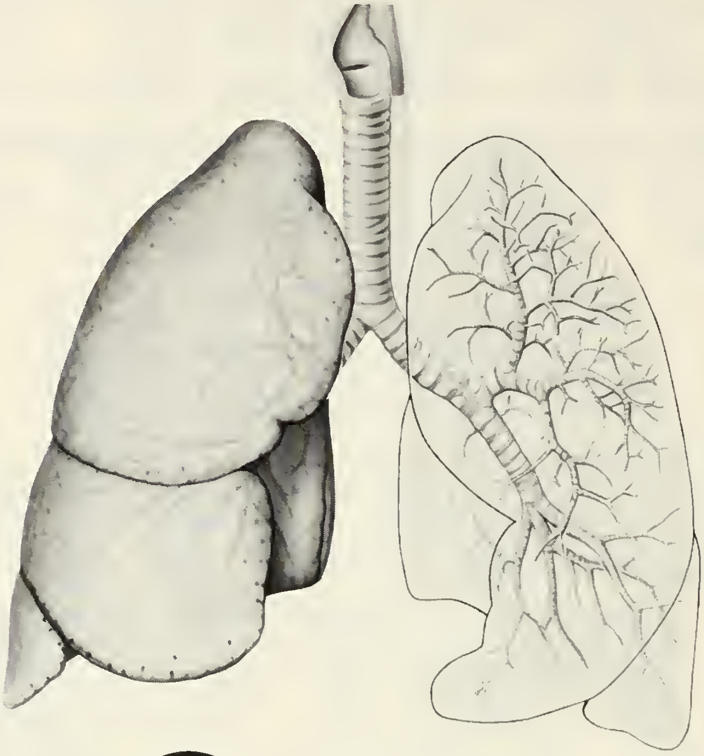

Ceclor®
cefaclor
250-mg Pulvules® t.i.d.

offers effectiveness against the major causes of bacterial bronchitis

H. influenzae, *H. influenzae*, *S. pneumoniae*, *S. pyogenes*
(ampicillin-susceptible) (ampicillin-resistant)

Brief Summary Consult the package literature for prescribing information

Indications and Usage Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae* and *S pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings IN PENICILLIN-SENSITIVE PATIENTS CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins) therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies and fluid, electrolyte, and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should be ruled out

Precautions *General Precautions* – If an allergic reaction to Ceclor® (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e g pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy – Pregnancy Category B – Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor® (cefaclor, Lilly) There are however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers – Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses Average levels were 0 18, 0 20, 0 21, and 0 16 mcg/ml at two, three, four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known Caution should be exercised when Ceclor is administered to a nursing woman

Usage in Children – Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1'5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain – Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic – Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic – Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal – Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

Note Ceclor® (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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Additional information available to
the profession on request from
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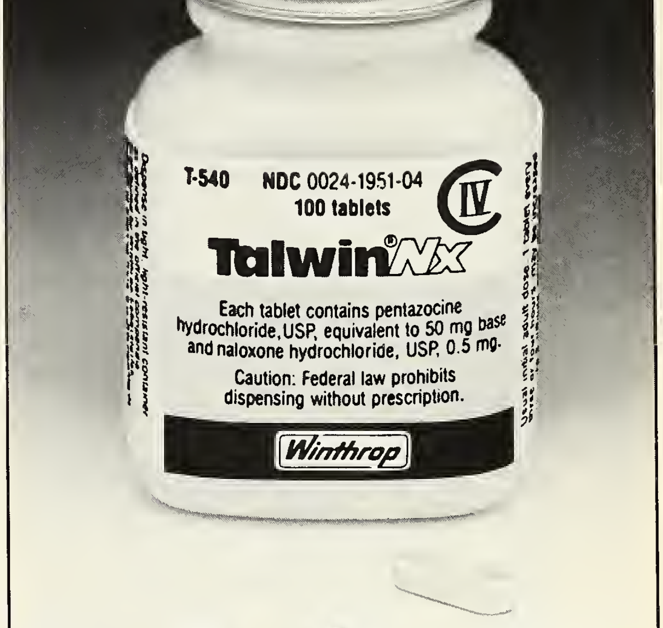
Now contains naloxone, a potent narcotic antagonist

Extra security added o proven efficacy and safety

No longer do doctors have to deny patients the enefit of an effective oral analgesic for fear of its nisuse by injection.

Winthrop-Breon Laboratories has met a nagging roblem by reformulating TALWIN® 50 (pentazoine HCl tablets) with the addition of naloxone, quivalent to 0.5 mg base. The reformulated roduct is called TALWIN® Nx.

The original formulation had been subject to a orm of misuse among street abusers known as "T's and Blues." TALWIN 50 and PBZ,* an antiistamine, would be ground up together, put into olution, and injected intravenously. The combiation produced a heroin-like high. Because aloxone is a narcotic antagonist when injected ntravenously, it acts to nullify any high a "T's and Blues" addict might expect from the pentazocine n a combination of TALWIN Nx and PBZ. When aken as directed orally, the naloxone component of TALWIN Nx is inactive. Thus, TALWIN Nx continues to be a safe, effective, oral analgesic for he relief of moderate to severe pain, now providng added security against misuse.



Registered trademark of Ciba-Geigy Corp for tripelennamine.

Talwin® Nx

(IV) Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0.5 mg base.

The reformulation of Talwin 50 to Talwin Nx involved the addition of 0.5 mg naloxone to help prevent misuse by injection.

Winthrop-Breon

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Please see following page for Brief Summary.

Talwin® Nx Ⓒ IV

Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0.5 mg base

Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone

> TALWIN® Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances (See **Drug Abuse and Dependence** section)

Warnings: *Drug Dependence* Can cause physical and psychological dependence (See **Drug Abuse and Dependence**) *Head Injury and Increased Intracranial Pressure* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention, these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure Can obscure the clinical course of patients with head injuries, in such patients, use with extreme caution and only if deemed essential. *Usage with Alcohol* Due to potential for increased CNS depressant effects, alcohol should be used with caution *Patients Receiving Narcotics* Pentazocine is a mild narcotic antagonist Withdrawal symptoms have occurred in patients previously given narcotics, including methadone *Certain Respiratory Conditions.* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis

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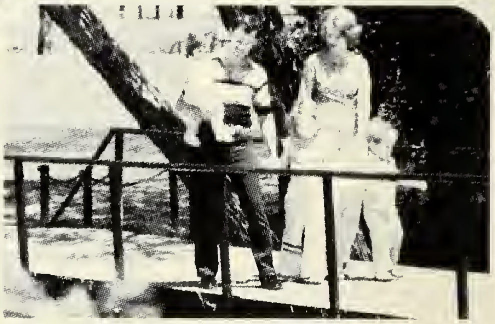

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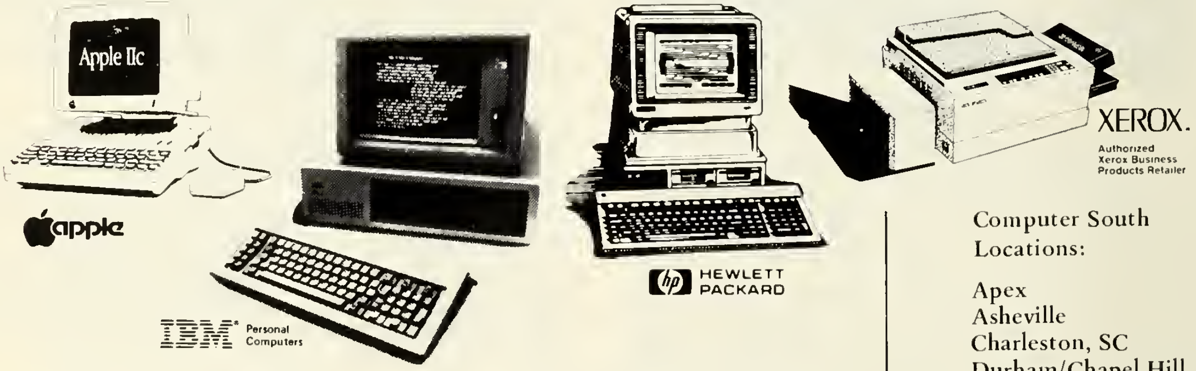

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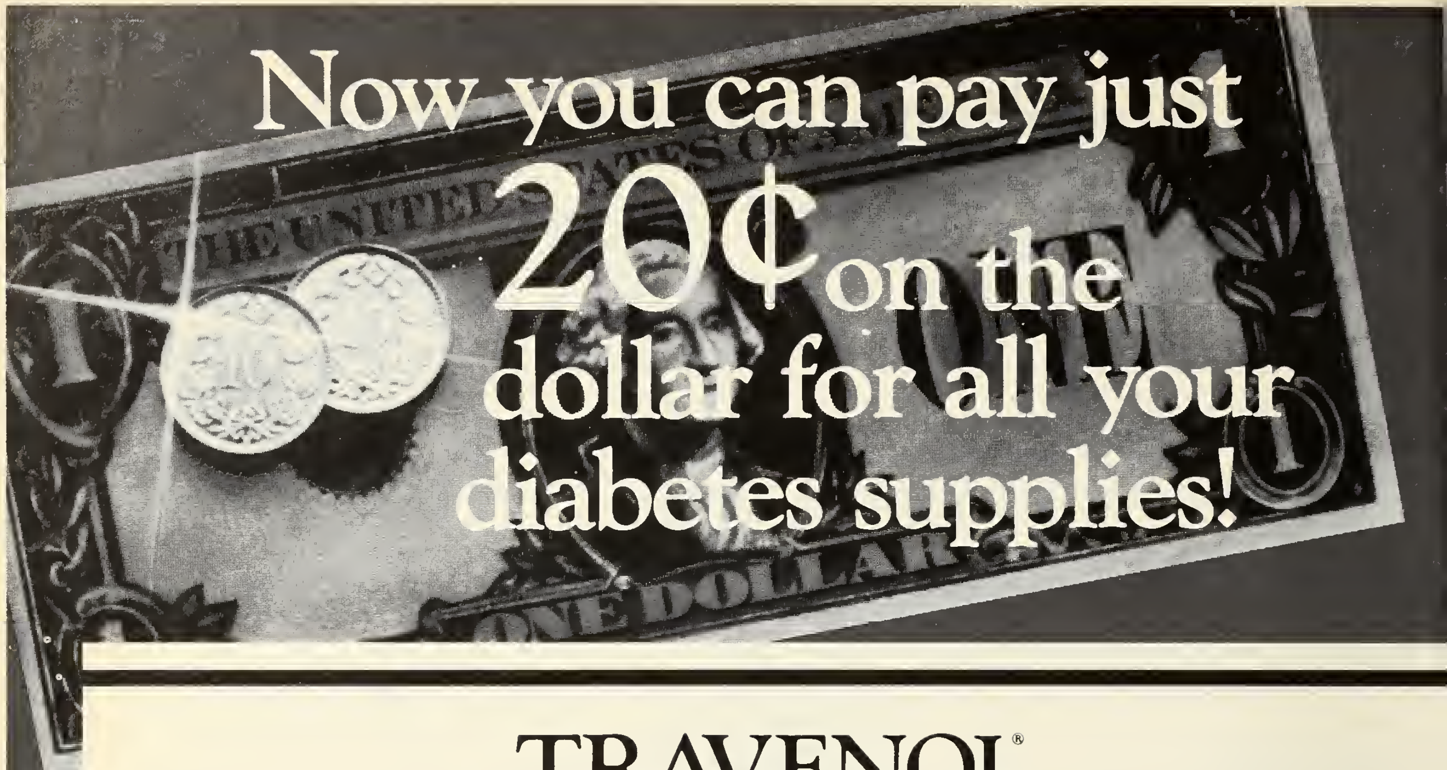

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Protesting the Proposed Federal Regulations for Critically Sick Infants

Loretta C. Kopelman, Ph.D.

• *Regulations proposed by the Department of Health and Human Services to implement the "Baby Doe" provisions of the 1984 Child Abuse and Treatment Act undermine the physician's ability to act in the best interest of the patient.*

MANY members of the Greenville, North Carolina medical community protested a recent and unprecedented attempt by the Department of Health and Human Services to restrict those practicing medicine and keep them from acting in what they believe is the best interest of their patients. The protest against proposed federal rules and guidelines regarding the treatment of severely ill newborns[1] was conveyed by letter to the Department of Health and Human Services. How many actually signed the letter is uncertain. More than 100 copies of it were distributed; some were duplicated, and many were sent with 10 to 30 signatures. I believe several hundred people signed, most of them physicians and medical students.

My purpose in writing this article is to record this protest publicly and permanently, to clarify why I wrote the letter, and to ask others to join us in protesting the proposals. In calling attention to why this letter was drafted, perhaps it will also illuminate why so many within the community were willing to sign it.

Briefly the background is this: The Child Abuse Amendments of 1984 were made to the Child Abuse Protection and Treatment Act, a federal law passed in 1974 establishing the National Center on Child Abuse and Neglect in the Department of Health and Human Services.[2] According to the new amendments, state-based child protection services could investigate charges that severely handicapped infants were suffering medical neglect. The formation of Infant Care Review Committees was strongly encouraged to guard against such neglect and to allow child protection services to work with Infant Care Review Committees. The 1984 Amendments attempt to clarify appropriate services and treatment for disabled infants. They were a compromise worked out by many interested organizations including the American Academy of Pediatrics.[3] These 1984 amendments circumvented a controversial series of attempts to formulate policy through an existing law, Section 504 of the Rehabilitation Act.[4] (A brief summary of these events may be found at the end of this paper.)

Our protest does not concern the law, the 1984 amendments to it or the events leading up to it. Rather, it focuses on the Department of Health and Human Services' efforts to *implement* these new statutory provisions of 1984 by offering rules, definitions and model guidelines for health care providers to establish Infant Care Review Committees. These proposed rules and guidelines for health care providers to establish such Committees, to which we protest, were published on December 10, 1984. The Department of Health and Human Services accepted and recorded comments until February 8, 1985. The new rules and guidelines, however, do not go into effect until six months after publication. With enough protest, we hope they will not go into effect at all. For, however well-intentioned, they could violate an ancient Hippocratic duty to act in the best interest of patients.

I will begin by first reproducing the letter. Second, I will show how I believe the proposed regulations alter the law by offering a different standard, one with less protection to infants singly and collectively. Next the Infant Care Review Committee proposed rules are criticized, and some observations are made about how the proposed rules, unlike the 1984 Amendments, are out of phase with recent important court rulings. The letter follows.

National Center on Child Abuse & Neglect
U.S. Children's Bureau, HHS
P.O. Box 1182
Washington, D.C. 20013

Attention: Jay Olson
Re: Child Abuse and Neglect Prevention and Treatment Program Proposed Rules — Part 1314 (Amended) Issued Dec. 10, 1984

Dear Sir:

This letter conveys opposition to many of the regulations proposed by the Department of HHS to implement the "Baby Doe" Provisions in the Child Abuse and Treatment Act. Our objections are similar to those of the American Academy of Pediatrics and the response drafted by the State of North Carolina, Department of Human Resources, under Secretary Phillip J. Kirk, Jr.

First, we are concerned the HHS definitions distort the law:

(1) **Virtually futile** — The HHS definition of virtually futile treatment is that it is "highly unlikely to prevent imminent death." Inclusion of the word "imminent"

From the Department of Medical Humanities, East Carolina University School of Medicine, Greenville 27834.

goes beyond the law and would require the treatment of an infant, for example, with Trisomy-13, who would die within a month to a year. It should be largely at the discretion of the physicians and the parents to determine whether fully treating such an infant would be in the infant's best interest.

(2) **Life-threatening condition —** The HHS definition of this stipulates that treatment may **not** be withheld "on the grounds that one or more of the infant's nontreatable conditions, although not imminently life threatening, will become life threatening in the future." The word "imminently" amends the law and should be omitted from the definition. For, once again, if the condition of the infant will become life threatening within the forseeable future, then physicians and parents should have the discretion to decide whether full treatment is in the best interest of that infant or will impose inhumane suffering on that child. Inclusion of the word "imminently" limits the range of these judgments.

(3) **Treatment —** The definition expands the intent of the law by including omission of further evaluation as a failure to treat. This again amends the law and restricts the discretion of parents and physicians.

Second, we are concerned about the Infant Care Review Committee guidelines.

(1) The basic functions are said to be optional yet the model is drawn in great detail and the words to describe its functions are "must" and "shall." This creates the false impression that ICRCs are mandated and the given form is prescribed by law.

(2) The functions are so broad that they could require a paid staff.

(3) It is uncertain how established rules of confidentiality and liability apply to the ICRC proceedings.

Third, the "Baby Doe" rulings coupled with the concerns over malpractice, have resulted in the tendency to treat even infants with the most futile prognoses. We are finding most intensive care nurseries filled with very small premature infants whose prognosis is grim, while infants with good prognoses do not get treatment because there is no room for them in the intensive care unit. While hospitals or intensive care units have no strict legal obligation to infants who are not in their units, reason would suggest that some consideration be given to infants who would profit from intensive care by having their lives saved or saved from the ravages of retardation and other handicaps, but who cannot gain access to care.

Fourth, the cost of caring for infants slowly dying over weeks and months in the NICU is great in terms of harm to these infants through their suffering, harm to the infants who cannot gain access to any NICU, harm to the families who watch them suffer and harm to the staff who witness these tragedies. The financial cost is also great, measurable in multiples of tens of thousands of dollars. With limited budgets this has the consequence of making less available to babies whose conditions can be helped, or whose conditions are serious but not life-threatening.

We urge you in the strongest possible way to allow more discretion to parents and physicians in choosing how to provide the most humane treatment for each infant, and acting in each infant's best interest.

Sincerely yours,

Name: Affiliation:

Different Standards

The 1984 Amendments, unlike the proposed regulations to implement them, allow the family and physician some discretion in deciding what is the best interest of a severely handicapped infant. According to the proposed rules, treatment may be withheld from a severely handicapped infant only if the death is imminent or the infant is irreversibly comatose. In contrast, the 1984 Amendments would also allow treatment to be withheld if it would not correct the underlying life-threatening condition, or if in terms of overall harms and benefits the treatment would be virtually futile and inhumane. The law uses a form of the *Best Interest Standard.* According to a Best Interest Standard those deciding for incompetent persons who were never competent should determine as best they can what the interests of the person are and, of those interests, which are most important in terms of the incompetent person's total well-being. When treatment is more of a burden than a benefit, then whether death is imminent or foreseen, it may not be in the best interest of the infant to treat fully. When employing the Best Interest Standards, therefore, one may properly consider whether a somewhat longer life in the Neonatal Intensive Care Unit (NICU), but one filled with suffering from the use and resulting complications of its technical resources, is in the best interest of a very handicapped child; or whether a shorter but more comfortable existence, perhaps closer to the child's family, is in the infant's best interest. Using this standard, it is legitimate to inquire whether it is in the overall best interest to fully treat an infant with Trisomy-13 or a premature infant weighing 700 grams who has had severe intracranial bleeding. Determining the net benefit includes judging if the discomfort of treatment and possible complications from using this technology are harms justified by a long range good for the infant.

The Best Interest Standard, therefore, allows consideration of an array of beliefs, values and preferences. The protection to the infant, however, is that this standard is restricted because its primary focus is on the infant's well-being or rights, and not what overall benefits society or the family might have. Moreover, when applied to infants this standard tends to be especially conservative. Incompetent adults may have expressed values or preferences the surrogate is honor-bound to consider. This is obviously not possible for infants, and in using it as an objective standard, we can only estimate what most would consider reasonable. The Best Interest Standard, however, does allow equity or consideration of the special features of each case in applying rules. It allows us to say what is best for *this* child in *this* situation. And insofar as we can reasonably rank important beliefs, values and preferences somewhat differently, this standard permits the possibility of somewhat different reasoned responses about what is in a person's best interest.

In contrast to this, the definitions proposed by the Department of Health and Human Services change the 1984 Amendments by offering a very different standard which permits little or no discernment or discretion in its application. This ruling as implemented by these proposed definitions allows withholding or withdrawing of treatment only where death is imminent or the infant is irreversibly comatose. Little discretion is permitted to families or physicians, and no consideration may be given to the severity of unavoidable and sustained pain.

Less Protection for Each Infant

Even if we agree that the 1984 Amendments and the definitions to implement the law proposed by the Department of Health and Human Services employ different standards, then what practical difference does this make? Both seek the protection of infants. But protection on each standard means different things. According to the 1984 Amendments, the Best Interest Standard allows protection to include a variety of interests including how much suffering is likely from a somewhat longer existence. On the other hand, the proposed definitions recognize protection to mean only one thing: saving all who can possibly be saved up to the limit of technology unless their death is ''imminent'' or they are permanently comatose. A standard emerges from these proposed rules that is problematic. Though death may be foreseen, overtreatment and overevaluation of infants may be required by law simply because death cannot be known to be ''imminent.'' More basically, however, it disallows the wide considerations possible using the Best Interest Standard. If we agree, however, that a life filled with pain is worse than one filled with happy experiences, and a life filled with potential is better than one that is not, then we can legitimately consider that a short comfortable life, perhaps at home or free from invasive painful technology, would be better than a somewhat longer, painful one. If so this would allow considering that it is in someone's best interest to forego full treatment.

Therefore, the Department of Health and Human Services' definitions distort and amend the law by offering a different standard for the treatment of handicapped infants. In addition, the Department's standards are unjust because they allow parents and physicians no opportunity to consider important features of the situation, such as how much suffering the baby will be forced to endure, in making their judgments.

It is disturbing to be kept from acting in a way one believes is in the best interest of the patient because the patient objects to treatment or because there is no treatment available. But it is more distressing when restrictions intended to protect cause harm. What is deeply troubling about the proposed rules is that, however well intentioned, they seem to violate the ancient Hippocratic moral rule to try to act in the best interest of one's patients. This moral duty and the standard offered by the proposed rules can conflict when considering the best interest of infants singly and collectively.[5] How would these proposed rules affect sick infants as a group?

Scarcity and Protection of All Infants Collectively

If the goal is to protect all handicapped infants collectively as well as each individual patient singly, the intent of the 1984 Amendments has been defeated by the proposed rules of the Department of Health and Human Services. Physicians and hospital administrators, mindful both of malpractice litigation and of federal laws and guidelines, are inclined now to overtreat or overevaluate all infants, even those with the most futile prognoses. The consequences are that most neonatal intensive care units are filled with such infants slowly dying, and infants with good prognoses cannot gain access to these units. Intensive care may be thought of as a ''scarce resource,'' and we have to determine how best to distribute it among a population. Is it reasonable to insist that the baby born with Trisomy-13 or severe intracranial bleeding, who we know will die but whose death is not ''imminent'' must, in spite of the good will judgments of parents and physicians, be fully treated over weeks or months until his death is ''imminent''; while an infant with a good prognosis who, with a few days in the nursery, might lead a healthy normal life must be denied?

Infant Care Review Committee

The Department of Health and Human Services has also recommended *as optional* the formation of ethics committees or Infant Care Review Committees. State-based child protection services would seek the assistance of such a committee to investigate charges of medical neglect. The Department uses great detail to present one particular model for the Infant Care Review Committee. This detail and employment of the language of ''must'' and ''shall'' tend to defeat the comment that such committees are optional, giving the false impression that the form and duties of these committees are prescribed by law. In reading these proposed guidelines, one is reminded of the committees required to review all proposed human research at institutions receiving federal funds. *If* the Infant Care Review Committee were like these Institutional Review Boards, then each committee would be legally obligated to review, approve or disapprove life and death decisions just as Institutional Review Boards must approve or disapprove research projects. That is, the Infant Care Review Committee in these proposals appears like a watchdog committee required to ''pass'' on each ''proposal'' like the Institutional Review Board.[6] But this seems quite inappropriate especially since the courts have repeatedly argued that the primary decision maker for judging the well-being of incompetent persons is the parents with the advice of the physician.

It is useful to have committees that will help to form policy and educate, to offer assistance to physicians and families in making these decisions, to consider the alternatives, prognosis, and resources in a particular situation, and to help those with questions of certain sorts. In an area where so little has been done, however, we should want many models tried, in the hope that from the variety we will learn what tends to work. It seems likely to me that the best committees will focus on what is the best for the infant. Fear of litigation and malpractice, however, could distort these judgments. Therefore some states, such as Arizona, have taken the additional step of making it possible for these committees to function without such fears by allowing the members of these committees immunity from prosecution, and mandating that its records and deliberations are nondiscoverable.[7]

It is disturbing when the judicial and administrative branches of government seem to recommend different standards as policy. In proposing to implement the 1984 Amendments with such restrictive rules the administration moves to *reduce* the discretion of families and physicians in making decisions for incompetent individuals. The New Jersey Supreme Court in January 1985 moved to *extend* their discretionary power. The New Jersey Supreme Court, which in 1976 allowed Karen Ann Quinlan to be removed from a respirator, handed down another landmark and controversial decision regarding Claire C. Conroy. In the Quinlan case the court argued that all life support can be withheld from incompetent as well as terminally ill competent patients, provided that is what the patient wants or would want. In the Conroy case the court reversed a ruling by the lower appellate court which had ruled that removing the feeding tube of an 84-year-old patient named Claire C. Conroy would have constituted homicide. Ruling 6 to 1, the justices said it was not homicide and clarified how the decision to stop treatment may be made for elderly, terminally ill patients, particularly those in nursing homes. The court said that when the patient's wishes cannot be determined, the family and physician should consider whether life-sustaining treatment would place burdens on the patient that outweigh the benefits derived from life and also whether the pain suffered would be ''inhumane.'' This extends the discretionary power of families and physicians. In the past the law had applied only to individuals who are brain dead or who, like Karen Quinlan, are irreversibly comatose.[8]

The Conroy Court reaffirmed the discretionary power of the family and the physician, and the person's right to refuse all medical care even at the risk of death, and found there is no difference in principle between the decision to begin treatment and the choice to stop it. The Court argued that physicians should not be fearful to discontinue respirator therapy once it has been started if discontinuing the therapy is in *the best interest of the patients.* The Court ruled that drawing a sharp line between feeding and providing other kinds of care may be inappropriate. While the Conroy Court is not meant to apply to newborns, it raises some important questions. First, if we should not discriminate on the basis of age, then we should either allow non-treatment of severely compromised infants if it is in their best interest to do so, as we do for elderly incompetent persons, or we should insist that all be treated unless their death is ''imminent'' no matter how much they suffer. Second, the Conroy Court distinguishes several Best Interest tests, one of which is similar to that discussed herein. This test, called the Pure-Objective test (unlike the limited-objective and subjective tests), has no evidence to consider about what the individual would have wished, but can only consider if the benefits of treatment outweigh its harms or if ''the recurring, unavoidable and severe pain of the patient's life with the treatment should be such that the effects of administering life-sustaining treatment would be inhumane.''[9]

Third, the Conroy Court is from New Jersey, and New Jersey led the way in the formation of ethics committees following the Karen Ann Quinlan decision. The Quinlan Court ruled that an ethics committee would be of value in New Jersey hospitals to determine the accuracy of the diagnosis and prognosis and to help spread the responsibility for these difficult decisions. These committees have worked well, perhaps because they are seen as a resource for families and physicians and because they are protected by the courts. The Conroy Court has ruled ethics committees may use these Best Interest tests.[9]

The Conroy Court gives importance to the Best Interest Standard and allows it to be applied in several different ways. It seems compatible with the 1984 Amendments to the Child Abuse and Treatment Act, but incompatible with the standard offered by the Department of Health and Human Services' proposed rules. In protesting the newly proposed definitions and guidelines, we suggest the proper standard to use is that of trying to do what is in the best interest of the incompetent person.

Although the time for official comment on these proposed regulations to implement the Child Abuse Prevention and Treatment Act has passed (the deadline was February 8, 1985), perhaps it will still be useful for others to make their views known.

*Brief Background**

1973	Rehabilitation Act containing Section 504 signed into Law by President Gerald Ford. (P.L. 93-112.29 U.S.C. 74)
1974	Child Abuse Protection and Treatment Act signed into law by President Ford establishes the National Center on Child Abuse and Neglect. (P.L. 93-247, 42 U.S.C. ''5101 et seq.)
May 18, 1982	Rehabilitation Act of 1973 was used as a legal basis for the HHS Notice to Health Care Providers in 6800 hospitals.
March 7, 1983	HHS publishes the ''Interim Final Rule'' in *Federal Register.* They take effect March 21, 1983.
April 14, 1983	American Academy of Pediatrics vs Heckler. No. 83-0774, U.S. District Court, D.C. Judge G. Gesell of the US-DC Court invalidates the interim ruling because: 1. the time required for comment was denied; 2. no definition is given of the ''customary medical care''; 3. it is ''arbitrary and capricious'' in failing to consider existing means of protection; 4. the free hotline is ''ill-considered'' and ''open to misuse''; 5. the investigators might jeopardize quality NICU care.
January 12, 1984	HHS publishes Final Rules in the *Federal Register* ''Nondiscrimination on the Basis of Handicap; Pro-

	cedures and Guidelines Relating to Health Care for Handicapped Infants'' (Vol. 49:8, 1622-1654).
February 23, 1984	U.S. Court of Appeals for the Second Circuit denied the government access to ''Baby Jane Doe's'' records.
March 12, 1984	The American Hospital Association brings suit in the U.S. District Court for the Southern District of New York, challenging the applicability of Section 504 of the 1973 Rehabilitation Act as the legal basis for the HHS rule.
October, 1984	President Reagan signs a compromise bill into law: Child Abuse and Neglect Prevention and Treatment Program. The 1984 Amendments to the Child Abuse and Treatment Act of 1974.
December 10, 1984	The Department of HHS proposes rules to implement this law.

* Some references to read for a fuller background are: President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research *Deciding to Forego Life-Sustaining Treatment.* Especially note the chapter, ''Seriously Ill Newborns,'' pp. 197-229. AND Weir, R. *Selective Treatments of Handicapped Newborns.* Oxford University Press, Oxford, 1984.

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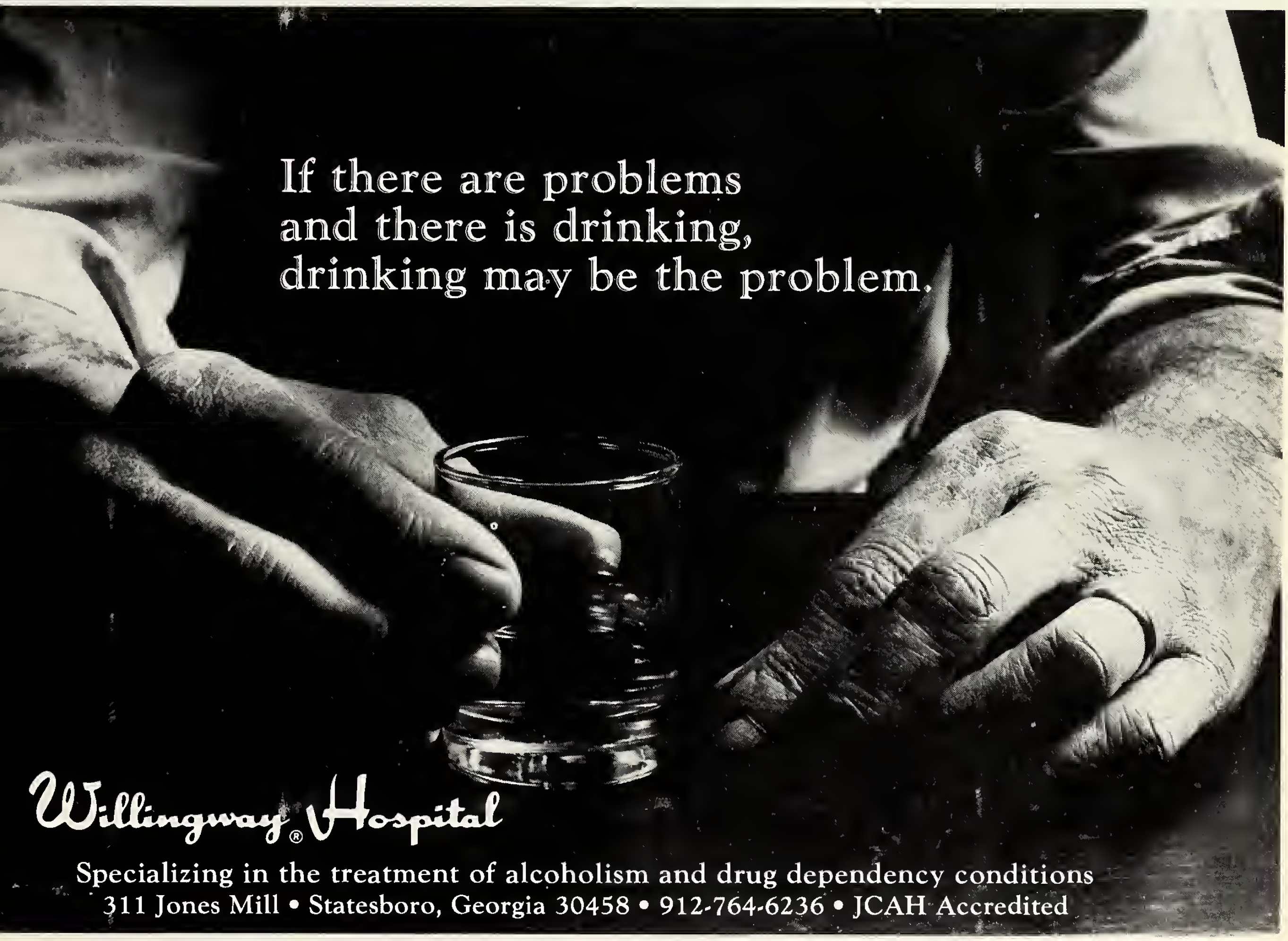

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Physicians' Forum: Medical Direction and Accountability for EMS Advanced Life Support Care in Rural North Carolina

Jane M. Hartley, M.S.P.H., Sandra S. Landis, R.N. and E. Jackson Allison, Jr., M.D., M.P.H.

- *How ECU's Emergency Medicine Department overcame the problem of involving area physicians in the development of a rural emergency medical services system.*

TO develop medical leadership and cooperation for prehospital emergency medical services in a 29-county area of eastern North Carolina: this was our assignment. The first move was to establish a non-profit organization, Eastern Carolina Emergency Medical Services, Inc. (ECEMSS), to raise funds for the venture. Federal dollars were obtained by June 1981.

A review of the geography emphasized the magnitude of the problem. The 29 counties cover approximately one-third of the state and measure roughly 150 miles from north to south and 160 miles from east to west at their most distant points, or approximately 13,736 square miles. The latest census has shown the population to be fairly stable at just over one million. Population is sparse in the majority of these counties with the average density being less than 75 people per square mile.

Approximately 35 percent of the total population is non-white with a low socioeconomic status, which is highly correlated with poor health.[1] Chronic illnesses and emergency cases put a strain on the emergency medical system and the region's hospitals.

Within the area are 23 general hospitals with various levels of emergency department coverage. In general, there is only one hospital in each county and the advancement of emergency medical services is not high on its list of priorities. Thus, between volunteers who do not have the training and equipment and hospitals that lack many necessary equipment and personnel requirements, advanced life support in the region has developed very slowly.

To develop medical leadership and cooperative efforts between hospitals and emergency services, the non-profit corporation and the Department of Emergency Medicine at East Carolina University School of Medicine co-sponsored a quarterly evening gathering called the "Physicians' Forum." The initial group that was invited included individual physicians who had assumed key roles in established EMS advanced life support programs. As medical directors and chairmen of audit and review committees, these physicians had been willing to get involved with their local rescue squads and hospitals to ensure that the programs were organized and initiated.[2]

At the first gathering, which was held in February 1981, there were physician representatives from the seven counties participating in EMT-I programs. All seven programs were comprised of volunteers or paid/volunteer memberships that had been trained to the EMT-I level by the Department of Emergency Medicine at East Carolina University School of Medicine. Each has one medical care facility, i.e., sponsor hospital,[3] in its respective county to which the majority of its patients are transported. All the programs were established under the Rules and Regulations, Mobile Intensive Care Program, North Carolina Office of EMS, and were certified by that agency. Yet with all these similarities, none of these physicians had met previously to share their experiences, especially in a group.

While the consensus is that emergency physicians make the most appropriate leaders in the field of EMS,[4] there is little opportunity for these individuals to acquire, much less to share, the necessary knowledge and skills outside of a designated emergency medicine residency training program.

The development of a successful EMS system profits by a cooperative arrangement between medical centers.[2] This requires an open dialogue, which became the first achievement of the Physicians' Forum. The physicians were able to compare notes and to discuss mutual problems without bureaucratic direction or guidelines. This prevented each program from wasting precious time trying to "reinvent the wheel." Instead, they hammer out the best way to solve programmatic issues together.[5] "A number of people throughout the country have the same instincts — it makes no sense to work [out problems] in isolation."[6]

Through the quarterly meetings held in the past four years, several regional issues have been identified as common concerns to all. Retrospective review of these topics finds that they logically fall into three primary categories: 1) communication channels with the North Carolina Office of Emergency Medical Services; 2) standardization of EMS system development; and 3) projects appropriate to EMS

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personnel in Area VI.

In North Carolina, the Office of Emergency Medical Services is charged with monitoring and enforcing the Rules and Regulations as promulgated by the State Board of Medical Examiners. NCOEMS also serves as the advisory organization to the Board of Medical Examiners.[7] Medical control in all ALS programs, therefore, is controlled by these two organizations. Before the advent of the Physicians' Forum, physician input from the field to these agencies had been sporadic, particularly in the East, and no clear avenue for expression of clinical concerns had been identified.

The disadvantages of lack of direct access to NCOEMS regulatory committees became obvious when the Forum members addressed a common clinical topic. The esophageal obturator airway had been accepted by NCOEMS for use by EMT-Intermediates, while the newer state-of-the-art adaptation, the esophageal obturator airway with gastric tube modification — the esophageal gastric tube airway — had been disallowed. This decision had eliminated physician option and control. Expressions of concern by individual physicians on the matter had been ineffectual; therefore, the Physicians' Forum decided to attempt a united statement to the Medical Director of NCOEMS. The result not only established a format for improved interchange, it also provided direction for future communications between both parties; in addition, the esophageal gastric tube airway was accepted by NCOEMS for EMT-I utilization.

Recognition of advanced life support personnel across county lines and co-sponsorship of advanced life support squads by two sponsor hospitals in the region were achieved through action by the Forum.

The second category of issues dealt with the standardization and coordination of the EMS system development within the 29 counties of eastern North Carolina. Federal funding stressed the need for coordinated standards for emergency patient transfers between facilities and provided funds for the development of Emergency Patient Care Transfer Protocols. Several critical care consultants, one from each critical care category — emergencies related to poisonings, burns, trauma, neonates, cardiac patients, spinal injuries and behavioral disturbances — were hired to create germane protocols for the region. The Forum was used to obtain a review of these protocols by the physicians in the 29 counties.

During the preparation and review of these transfer protocols, several Forum members from the larger receiving hospitals expressed concern regarding the total absence of transfer agreements between hospitals in the region. Consequently, the group developed written and signed agreements between transferring and receiving hospitals which clarified necessary and expected transfer procedures, and thereby tightened a very haphazard system of patient transfer. The agreements did not, however, affect existing referral patterns. To create a standardized format, a subcommittee of the Forum was formed which developed an acceptable document for the 29 counties.

Upon the completion of the transfer protocols and transfer agreements, it was the consensus of the Forum that both documents would not be given due consideration if they were sent blindly to each of the 23 hospitals in eastern North Carolina; therefore, it was decided that Dr. Allison and other Forum members would take the documents to each of the area's medical staff meetings to promote understanding and acceptance through appropriate in-service. This process took much longer to accomplish than anticipated and resulted in a great deal of discussion among area medical staff members; however, the result was successful in alerting area physicians that such documents existed and why they were needed.

The need for special projects appropriate to EMS personnel was identified as the third category by the Physicians' Forum. Dedication to the development and coordination of educational opportunities is of foremost concern to all the Forum members; at the beginning of each Forum meeting formal presentations on various topics in emergency medicine for continuing medical education (CME) credit have been added. Furthermore, the scheduling of regular Advanced Cardiac Life Support and Advanced Trauma Life Support courses at East Carolina University School of Medicine has made these courses available for physicians throughout the region.

The Forum was effective in maintaining physician leadership in the use of military antishock trousers (MAST). In North Carolina the basic EMT is permitted to use MAST at his/her discretion as a treatment or stabilization modality. Although NCOEMS encourages medical direction prior to application of the garment in the field, there is no specific regulation specifying the clinical use of MAST in North Carolina. When the regional EMS Councils requested MAST training for their rescue squads, the Forum members expressed their concern about the obvious lack of medical control in the clinical application of the garment. Through a unanimous effort, all protocols for MAST now require EMTs to contact a physician prior to inflation.

The Forum members also participated in MAST in-service sessions which were conducted in three of the four planning regions. This exposure was the first participation many of the members had had with basic EMTs in an educational setting, and they became acutely aware of the real need for physician involvement with this group. The result has been for Forum members to identify area physicians who have shown some interest in the basic life support rescue squads, and to invite them to the Physicians' Forum. Through exposure to and encouragement from the members of the Forum, we hope that these physicians will continue to develop appropriate medical direction for basic rescue squads in eastern North Carolina. Also, more physicians are being invited to attend and instruct in the area's EMS seminars, increasing their visibility with the squads. Due to the size of the area, and the historical paucity of involvement by physicians, we expect that the process of re-education will keep the Forum members occupied for some time to come.

Prospects for the Future

As one might expect, new issues in rural EMS system development continue to surface.[8] Cooperation is a key component for success.[9] Presently the Forum is working with the effects of Level II (and eventually Level I) Regional Trauma Center Designation at Pitt County Memorial

Hospital; the loss of federal monies for EMS development; and the need for rapid transport (i.e., a helicopter service) for severely ill and/or traumatized patients. As in the past, these issues were regional in impact. Now, however, our 29 counties have an effective mechanism in place for their development, resolution and implementation.

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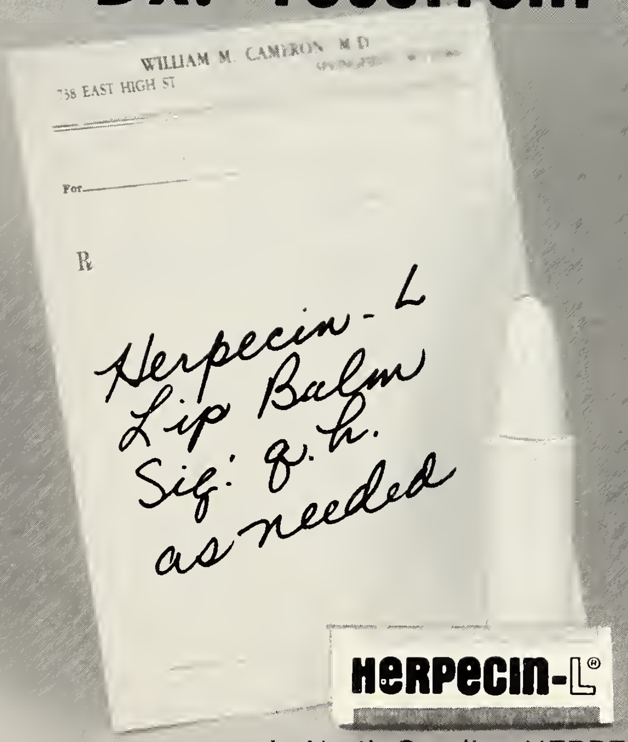

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The Impact of Prospective Payment for Physician Fees on Medical Specialists

J. Griffith Steel, M.D.

- *How will the medical profession respond when (or if) DRGs are extended to cover physicians' fees as they now cover hospital fees?*

WHEN President Reagan signed into law PL 98-21 on April 20, 1983, this Social Security reform bill revolutionized the manner in which the Federal government purchased health care for 30 million beneficiaries of Medicare. It ended the "cost-plus" method of reimbursement for hospital services under the Medicare insurance system and introduced a system of prospective payment in an effort to halt the rapidly spiraling costs of health care.

This article examines the impact of the Prospective Payment System (PPS) should it be extended to include payment for physician services and discusses possible adaptive changes in the practice patterns of medical specialists.

The Prospective Payment System

Part B of the Medicare Trust Fund, which reimburses physicians, is the third largest federal domestic program and is the fastest growing entitlements program. It has a compound growth rate over the last several years of 13%, double that of general inflation.[1] The causes for the explosion in health care costs have been extensively analyzed.[2-4] The aging population, increased societal expectations, improved treatment modalities, fear of malpractice, and lack of economic incentives for efficiency all contribute to price and service inflation.[3]

Public Law 97-248, passed in August 1982, ordered the Secretary of Health and Human Services to design and to send to Congress a new payment system for Medicare. On December 28, 1982, the Department presented its proposal (PL 98-21), the most important provision of which was that it fixed in advance a price that Medicare would pay a hospital to treat a particular disease. The impact of the PPS in the first year of phase-in has been significant. After rising more than 4% annually for years, Medicare hospital admissions remained flat at 8.8 million in Fiscal Year (FY) 1984, despite a 2% rise in the over-65 population (*Business Week,* October 15, 1984). The Medicare hospital budget estimates for FY 84 were revised downward from $41.7 billion to $39.6 billion. Average length of stay dropped from 9.4 days in July 1983 to 7.4 days in July 1984.

PPS for Physician Fees

Medicare and Medicaid spent 54 billion dollars, or 64% of its budget, for hospital services in FY 83. The remainder was spent on nursing care, rehabilitation, prescriptions, equipment, and physician fees. Aware that large aspects of the Medicare program remained uncontrolled, Congress required in PL 98-21 that the Secretary of Health and Human Services report on the feasibility of including physician fees under some kind of PPS. The Health Care Financing Administration is actively studying ways of bringing physician fees into a PPS. Brandeis University Health Policy Center is under contract to study whether physician fees should be included in the present Diagnosis Related Group (DRG) system. A study by Mandex, Inc. addresses the issue of how many physician charges before and after hospitalization should be included in a DRG. A system of classifying outpatients based on health resource consumption was developed at Yale University to serve the same purpose as DRGs.[5] Outpatient DRGs, known as "Ambulatory Patient Related Groups," incorporate factors that pertain to patient care, in addition to diagnosis. Fetter assessed 70 different variables to find the items that best explained the statistical variance in resource usage for a given diagnosis (Fetter RB: Ambulatory Patient Related Groups, unpublished manuscript, Yale University, 1980).[5] An APG classification system would allow standardization of payment for outpatient care.

In addition to developing a classification system for outpatients, the Health Care Financing Administration is studying new methods for distributing physician fees under a single-payee system. Options include the following:

1. pay the hospital the total service fee and let the hospital pay the physician his share;
2. pay the physician and let him return to the hospital its share;
3. pay the primary care physician the entire sum and let him distribute shares to the hospital and consultants.

Implications for Medical Specialists

Medical specialists constitute approximately 28% of all physicians (internal medicine, allergy, cardiovascular diseases, dermatology, gastroenterology, pediatrics, pediatric allergy, pediatric cardiology, and pulmonary medicine).[6]

From the Eastern Carolina Neurological Associates, Inc., 425 Stantonsburg Road, Greenville 27834.

Excluding the pediatric group, medical specialists spend 44% of their patient contact hours in the office and 26% in the hospital, compared with 58% and 15%, respectively, for general and family physicians.[7] They depend heavily on referrals from other physicians; internal medicine and its subspecialties (including neurology) see 63.7% of patients on referral, as opposed to 7% for family and general practitioners.[8]

Under a single-payee, fixed reimbursement system for physician fees there will be a strong economic disincentive for physicians to consult specialists. Hospitals, if allowed to keep part of the savings resulting from reduced physician costs, may hire more staff physicians in order to directly control physician services. Medical entrepreneurs have already used this economic incentive for their profit. Philadelphia-based United States Health Care Systems, Inc., a large for-profit HMO, monitors its physicians' use of specialists. If a physician can provide care without making referrals to specialists, some of the savings goes to him.[9]

Adaptations by Medical Specialists

Regardless of whether the payee is the hospital, a fiscal intermediary, or the primary care physician, consulting specialists will face a decline in demand for their services under a fixed-reimbursement, single-payee system. A number of adaptive changes are foreseeable.

1. **Growth of contract medicine.** Hospitals and physicians will join chains or organized groups.[4, 10] Specialty-based groups are likely to contract their services for a fixed fee in order to assure a patient population.
2. **Vertical integration.** Specialists will expand their services to retain patients who might otherwise be lost back to the primary practitioners. An example would be a cardiology group that offered outpatient diet counselling and cardiac rehabilitation, or a neurology group that expanded to offer office physical therapy.
3. **Horizontal integration.** Specialists will seek to attract outpatient self-referrals, by-passing the primary care physicians. An example would be a free hypertension screening clinic offered by a cardiology group, promoted by aggressive advertising.
4. **Increased medicine by protocol.** With revenues fixed for a given diagnosis, medical specialists within a community or provider group will work out agreed-upon standards of care to enforce uniformity and to maximize economic return. One partner's expensive idiosyncracies may not be tolerated by the group.
5. **Decreased purchase of new technology.** The absence of a mechanism for capital cost and new technology pass-through may act as a disincentive to invest in new equipment.
6. **Hospital substitutes.** One of the most radical and cost-saving innovations would be the creation of alternatives to hospitals for those patients requiring minimal supervision. Large referral specialty groups may invest in motels or apartments to house their out-of-town patients while they undergo diagnostic studies or outpatient treatments.
7. **Sole providerships.** Where possible, medical specialty groups may merge to eliminate competition and increase their bargaining power with fiscal intermediaries.

Comment

The success of the Medicare PPS will doubtless encourage Congress to order extension of the concept to cover physician fees. Beneficial effects include elimination of irrational variation in fees and elimination of excessive reimbursement for procedure-oriented as opposed to cognitive services.[11] A single-payee system will strengthen the role of the primary care physician as the gatekeeper of health services and may encourage medical students to choose family practice as opposed to one of the overcrowded specialties.

In response to the changing economic environment, medical specialists are likely to alter their practices to attract self-referrals, retain patients longer, eliminate competition, contract with large payer-organizations, and create alternatives to hospitals. Practice uniformity among members of specialty groups will be mandatory to minimize costs. However, a physician-PPS which rewards primary care providers for not consulting is fraught with quality of care issues. Competition between specialists and primary care physicians for patients and increased malpractice costs may reduce savings expected from a Prospective Payment System for physician fees.

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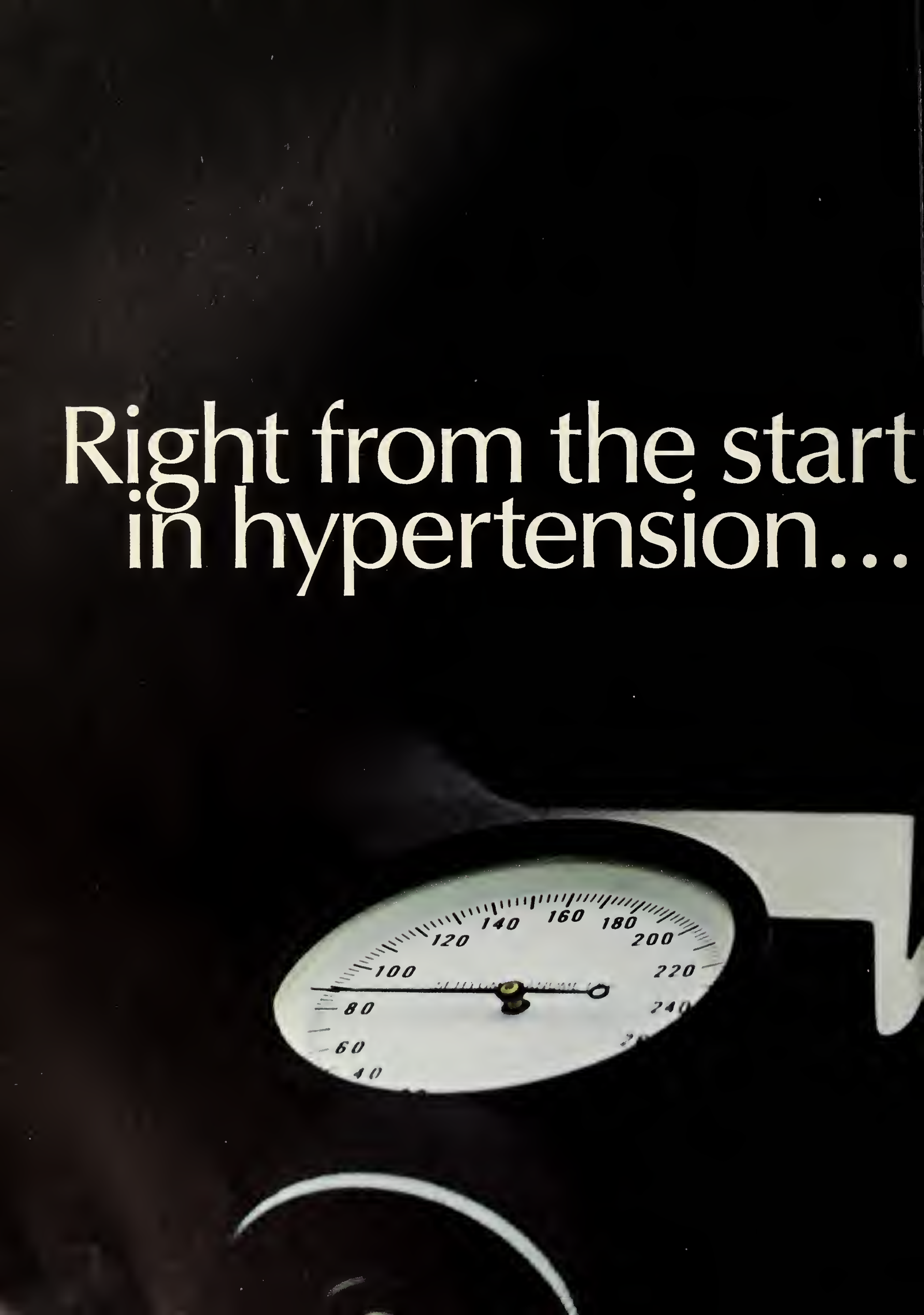
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60
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Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[1,2] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Please see brief summary of prescribing information on the next page for further details.

For beta-1/beta-2 blockade

Once-daily INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use Effects on plasma volume appear to be minor and somewhat variable INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmias is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient But there are also situations in which sympathetic stimulation is vital For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

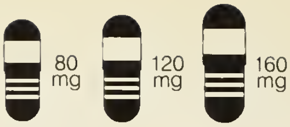
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures



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INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular bradycardia congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—-80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

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The Dark Night of The Soul — Disulfiram Toxicity

Ronald B. Mack, M.D.

HAVE you ever fantasized that you would have liked to live in an earlier time in history? I bet you have! No, I don't mean reincarnation — I mean thinking about what it would have been like to live in the Golden Age of Pericles or the Renaissance or to have worked with Pasteur. I have many favorite eras that I would like to have lived in, but one of my most fervent desires would be to have been a young adult in the 1920s. For example, I could have helped my father in his troubles with the gangs of Bugsy Moran and Al Capone in Chicago — the "beer wars," the "territorial wars" terminating in the St. Valentine's Day Massacre. I could have frequented "speakeasys," danced the Charleston, swallowed goldfish and dated a "flapper" (for those of you who do not understand this, ask your parents or grandparents).

The author who probably fictionalized this era the best was F. Scott Fitzgerald. He personified in his writings and lifestyle the Roaring Twenties, the Jazz Age, the age of America's adolescent rebellion. It was that time after World War I when our country lost some of its innocence. Many of the authors of that time (Hemingway, Fitzgerald, etc.) attempted to chronicle what came to be known as The Lost Generation.

As with many authors of his day, Fitzgerald lived fast, consumed far too much alcohol and did it too often and died too young. It seems that World War I erased many of the conservative pre-war mores in lifestyle and literature. One of his most memorable pronouncements was, "In a real dark night of the soul it is always three o'clock in the morning, day after day." Haven't we all at some time or another found ourself awake at 3:00 am in bed staring into the darkness and having all of our fears inordinately exaggerated? F. Scott Fitzgerald, to my knowledge, did not take disulfiram (Antabuse) to ease his problem with ethanol and he apparently experienced "dark nights of the soul" too numerous to count.

Disulfiram is used by almost a quarter of a million alcoholic patients. It is an aversive drug, which means that if you take it and then consume alcohol you get about as sick as you ever want to be. As with a great many scientific advances this product was discovered by accident. Two Danish physicians were investigating disulfiram's use as a potential antihelmintic. They took some of the drug themselves (Why?) and then proceeded to go to a cocktail party. You can guess the end of the story; the rest is history, as they say.

When someone imbibes ethanol, the liver normally metabolizes it by reducing serum levels approximately 15 mg/dl per hour and produces *acetaldehyde* which is a toxic intermediary metabolite. This acetaldehyde is then metabolized by aldehyde dehydrogenase. Disulfiram acts by inhibiting hepatic aldehyde-NAD oxidoreductase (Gosh, I didn't know that, did you?) causing great increases in blood acetaldehyde levels following ethanol ingestion. When you administer ethanol to someone who has been pre-treated with disulfiram the blood acetaldehyde concentration rises five to ten times higher than someone who does not have Antabuse on board. So what — you may inquire!! Well, the effect can be devastating and one of the names of the condition it causes is the *acetaldehyde syndrome* — surely "a dark night of the soul."

Within minutes after imbibing ethanol the disulfiramized patient wishes he or she could enter a time warp and undo this unforgettable event (please remember that we are not just talking about the swallowing of Jack Daniels or Coors, but many other sources of ethanol, e.g., there are over 700 pharmaceutical liquid preparations such as decongestants, cough medicines, etc. that contain ethanol as a solvent or diluent). After a few minutes, the victim experiences a hot, flushed face. Vasodilatation spreads to involve what seems like the entire body causing vigorous throbbing in the head and neck and a pulsating headache (worse than any "hangover" I'm sure). This is accompanied by respiratory difficulty, nausea, profuse vomiting, diaphoresis, chest pain, remarkable hypotension and orthostatic vertigo, diplopia and confusion. Shock would not be unusual. In addition to increasing the level of acetaldehyde, disulfiram is known to inhibit dopamine-beta-hydroxylase which causes a decreased production of norepinephrine in sympathetic nerve terminals and thus hypotension. As little as 7 ml of ethyl alcohol in a sensitive adult can cause a mild version of the above syndrome. This aversive response can last from 30 minutes to several hours. Sometimes the result is death.

Now what do you suppose happens when an adult drinks disulfiram in overdose and does not also drink ethyl alcohol!! This drug is rapidly and completely absorbed from the gastrointestinal tract. Approximately 50% of the drug and its metabolites are eliminated in the urine, feces and breath within 25 hours and after 6 days up to 80% is eliminated; it is highly lipid soluble. Taken by itself disulfiram can cause, in adults, urticaria, fatigue, tremor, reduced sexual potency, tremor, dizziness, epigastric pain, vomiting and diarrhea, a garlic-like taste — wow, am I glad to hear that, I thought it came from the vino rosso and the lobster fia

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From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

diavolo!! In general, in adults a single dose of disulfiram, in the absence of alcohol, usually does not produce noticeable side effects except possibly for an initial period of lethargy. On the other hand, carbon *disulfide*, a metabolite of disulfiram, can react with the coenzyme pyridoxine phosphate to inhibit the enzyme monoamine oxidase. Large overdoses of disulfiram (without ethanol) can cause choreoathetosis, a Parkinson-like syndrome and endocrine abnormalities as well as hallucinations and in severe cases coma and death from cardiovascular collapse. Many authors believe that carbon disulfide is responsible for these evil effects from a large disulfiram overdose.

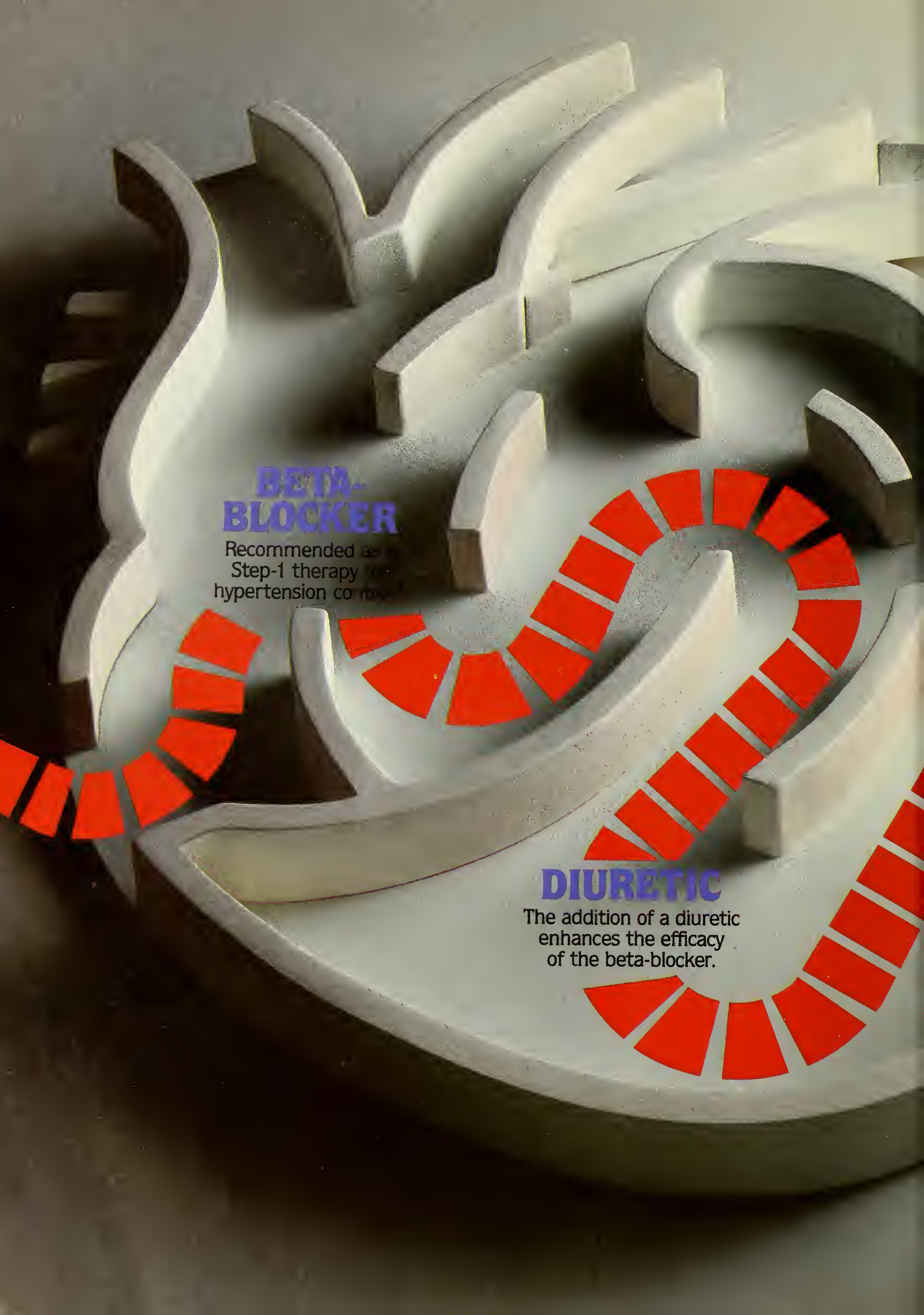
Finally, there is the problem of disulfiram overdose in a child. Is this a different syndrome than when an adult overdoses on the drug? To begin with, is this really a problem? Well, many alcoholic patients have children, many alcoholics are unemployed, have marital discord, have unstable life styles, and many alcoholics are on chronic disulfiram therapy; this adds up to a great potential for accidental ingestion of this drug by members of the preschool population. Disulfiram overdose in a child is different than in adults and according to the literature has generally a poor prognosis. Overdose of this drug by a child, after a lag time of as long as 12 hours, causes *vomiting, lethargy, hypotonia* which can progress to stupor or *coma* (sounds a bit like Reye's syndrome, doesn't it? However, ammonia and transaminase levels are normal). There is frequently in association with the foregoing: *dehydration*, pronounced *tachypnea* and *tachycardia* and *very poor muscle tone;* deep tendon reflexes are typically very decreased often to the point of being absent. *Ketosis* which is typically disproportionate to the degree of dehydration seems to be a fairly consistent laboratory finding. In adults, one sees more of a picture of bizarre thought processes, agitation and hallucinations with disulfiram overdose. On the other hand *stupor, weakness, hypotonia* and *coma* are rare in adults but almost the rule in *children*.

Without a very precise history, especially about the presence of alcoholics in the family who might be taking Antabuse, this is a difficult diagnosis to make. Disulfiram is not detected by the usual ''toxic screen.'' To confirm an overdose you need to obtain levels for disulfiram or its metabolites: diethylthiocarbonate and diethylamine and carbon disulfide. Needless to say, these levels are not available at most hospitals. Still another problem related to these levels is the fact that disulfiram is rapidly reduced in the patient and may be undetectable in serum soon after ingestion. The level of disulfiram or its metabolites does not correlate with the severity of intoxication anyway so don't feel badly if you cannot get them. Do what a good clinician always does: be a skillful data collector.

The treatment of disulfiram intoxication is not very thrilling and is mainly supportive; even elements of this supportive management involve controversy. For example, although gastric emptying is recommended early on, some authorities advise against the use of ipecac syrup because this product contains ethanol and could potentially precipitate an ethanol-disulfiram reaction. Gastric lavage would seem to be a safer choice. Although the standard gastrointestinal decontamination procedures of administering activated charcoal and cathartics are recommended, there are no good data that prove they make a difference. Some authors recommend the intravenous use of pyridoxine (as in INH overdose) if signs of neurological toxicity are present. The rapid absorption and high lipophilic potential of disulfiram make extracorporeal removal such as charcoal hemoperfusion, etc. an unlikely solution to the problem. Very clearly there is no antidote and you must treat the patient and not the toxin. An overdose of disulfiram in a young child can be devastating — the result could be severe brain damage or death.

I have often wondered what kind of a writer F. Scott Fitzgerald would have been if he had been a member of AA or had been on chronic disulfiram therapy. I hate to say this, but I would guess in his case art imitated life and he would probably have failed as a man of letters without his ''dark nights of the soul.'' For myself, iced tea or a glass of soda-pop seems to make a difference and this probably explains why I never make the *New York Times* best seller lists.

The Logical Path to Compliance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Recommended as a
Step-1 therapy for
hypertension control.
DIURETIC
The addition of a diuretic
enhances the efficacy
of the beta-blocker.

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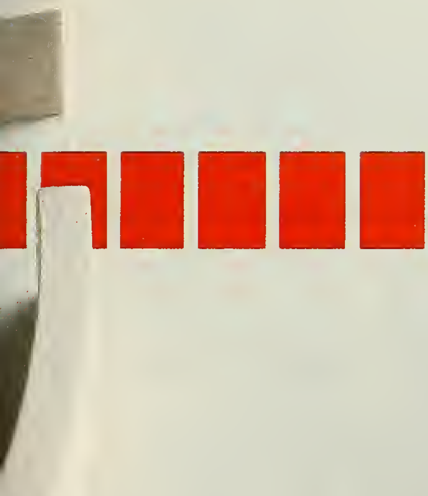

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(nadolol-bendroflumethiazide tablets)

Makes good sense

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SQUIBB
Innovators in cardiovascular medicine

*Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: The 1984 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 144:1045-1057, 1984.

Please see brief summary of prescribing information on following page

CORZIDE®

(nadolol-bendroflumethiazide tablets)

CORZIDE® 40/5
CORZIDE® 80/5
Nadolol-Bendroflumethiazide Tablets

DESCRIPTION: CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration combines two antihypertensive agents: CORGARD® (nadolol), a nonselective beta-adrenergic blocking agent, and NATURETIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations: 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide.

CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). **Bendroflumethiazide** — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs

WARNINGS: Nadolol — **Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually, if possible).

> **Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal** — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta_2 receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia, therefore, it may be necessary to adjust dose of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — **Nadolol** — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and G.I. disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather, appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary arter insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients bein treated with beta-adrenergic blocking agents to consult physician at the first sign or sympton of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS *Bendroflumethiazide*, and PRECAUTIONS, *General, Bendroflumethiazide*).

Drug Interactions — **Nadolol** — When administered concurrently the following drugs ma interact with beta-adrenergic blocking agents: **Anesthetics, general** — exaggeration o anesthetic-induced hypotension (see WARNINGS, *Nadolol, Major Surgery*). **Antidiabetic drugs (oral agents and insulin)** — hypoglycemia or hyperglycemia, adjust antidiabetic dru dosage accordingly (see WARNINGS, *Nadolol, Diabetes and Hypoglycemia*). **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect; monitor closely for evidence o hypotension and/or excessive bradycardia.

Bendroflumethiazide — When administered concurrently the following drugs may interac with thiazide diuretics: **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of antidiabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or peripheral adrenergic blocking drugs** — potentiated effect. **Preanesthetic and anesthetic agents** — effects may be potentiated, adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, *General, Bendroflumethiazide*).

Carcinogenesis, Mutagenesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed.

Pregnancy — **Teratogenic Effects** — **Nadolol** — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose, no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus, these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol-Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported, intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus, headache, dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness, sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol. The following adverse reactions may also occur: **Central Nervous System** — reversible mental depression progressing to catatonia, visual disturbances; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss; emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat, laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia, Peyronie's disease; erythematous rash; arterial insufficiency.

Bendroflumethiazide — **Gastrointestinal System** — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersensitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed. Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, employ the following measures, as appropriate. **Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation. **Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a beta_2-stimulating agent and/or a theophylline derivative. **Stupor or Coma** — Supportive therapy as warranted. **Gastrointestinal Effects** — Symptomatic treatment as needed. **BUN and/or Serum Electrolyte Abnormalities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

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505-502 Issued March 1985

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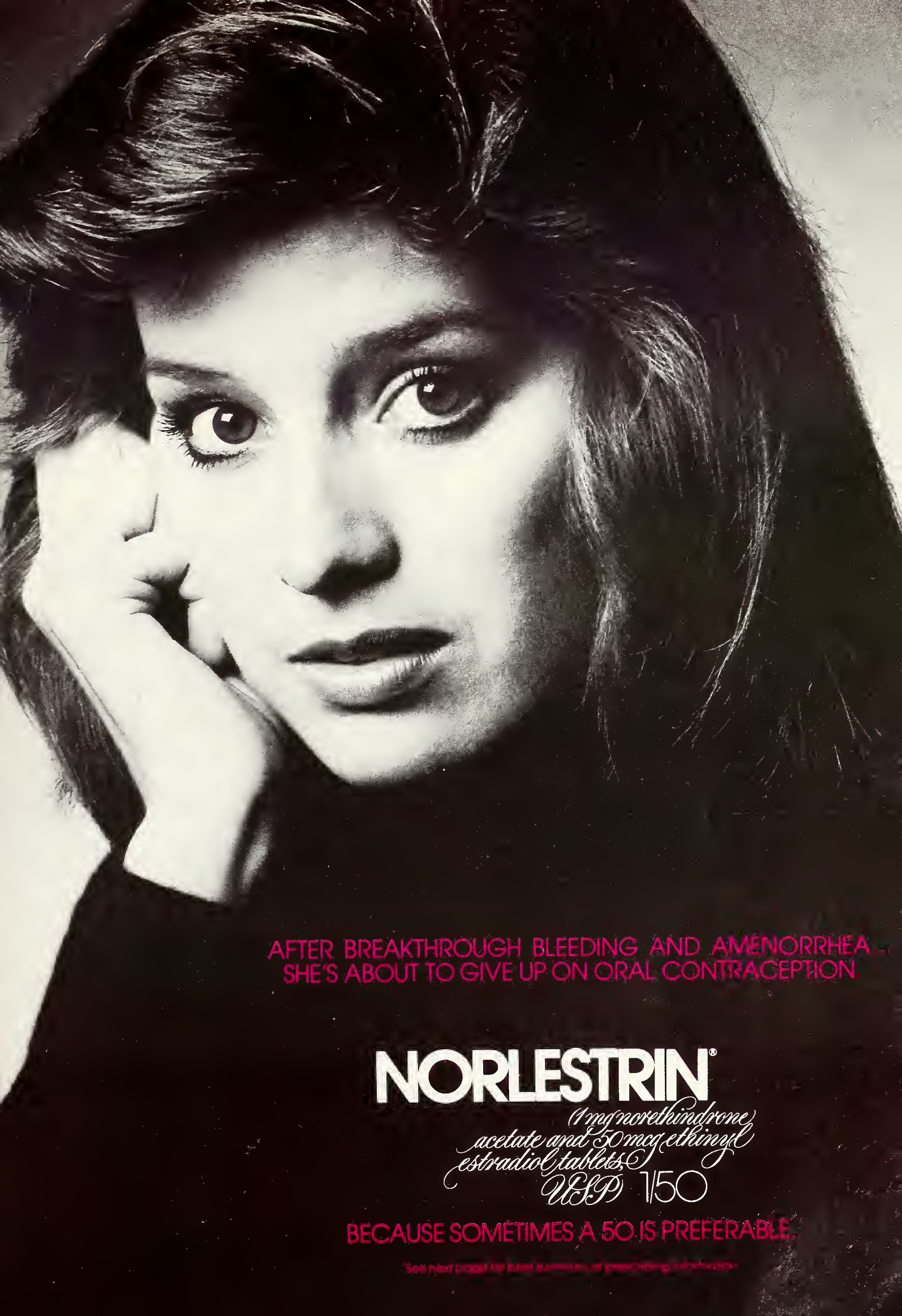

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NORLESTRIN®
(1 mg norethindrone
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USP) 1/50

BECAUSE SOMETIMES A 50 IS PREFERABLE.

See next page for brief summary of prescribing information.

Brief Summary of Prescribing Information

NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information A Brief Summary follows

DESCRIPTION

Norlestrin Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE

Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0 05 per 100 woman-years, in clinical trials with Norlestrin 2 5/50 involving 96,388 cycles, there was a pregnancy rate of 0 22 per 100 woman-years

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance

CONTRAINDICATIONS

1 Thrombophlebitis or thromboembolic disorders
2 A past history of deep-vein thrombophlebitis or thromboembolic disorders
3 Cerebral vascular or coronary artery disease
4 Known or suspected carcinoma of the breast
5 Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding
7 Known or suspected pregnancy (See WARNING No 5)
8 Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

WARNINGS

> **Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.**
>
> The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1 *Thromboembolic Disorders and Other Vascular Problems* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2 0 times greater in users than nonusers, and the risk of thrombotic stroke was 4 0 to 9 5 times greater

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not Oral contraceptives, however, were found to be a clear additional risk factor

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke The amount of smoking is also an important factor

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the guantity of estrogen may not be the sole factor involved

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders Should any occur or be suspected, the drug should be discontinued immediately

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization

2 *Ocular Lesions* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions

3 *Carcinoma* Long-term continuous administration of estrogen in certain animal species increases the freguency of carcinoma of the breast, cervix, vagina, and liver

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives Close clinical surveillance of users is, nevertheless, essential In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care

4 *Hepatic Tumors* Benign hepatic adenomas have been found to be associated with oral contraceptives Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives The relationship of these drugs to this type of malignancy is not known at this time

5 *Usage in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring* During early pregnancy, female sex hormones may seriously damage the offspring

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy

6 *Gallbladder Disease* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives

7 *Carbohydrate and Lipid Metabolic Effects* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives

An increase in triglycerides and total phospholipids has been observed

8 *Elevated Blood Pressure* An increase in blood pressure has been reported in patients receiving oral contraceptives The prevalence in users increases with longer exposure Age is also strongly correlated with development of hypertension Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure

9 *Headache* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, reguires discontinuation of oral contraceptives

10 *Bleeding Irregularities* Breakthrough bleeding spotting, and amenorrhea are freguent reasons for patients discontinuing oral contraceptives In breakthrough bleeding, nonfunctional causes should be borne in mind In undiagnosed abnormal bleeding from the vagina, adeguate diagnostic measures are indicated to rule out pregnancy or malignancy

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives

11 *Ectopic Pregnancy* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures

12 *Breast-Feeding* Oral contraceptives may interfere with lactation Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs

PRECAUTIONS

1 A complete medical and family history should be taken prior to the initiation of oral contraceptives The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination

2 Preexisting uterine leiomyomata may increase in size

3 Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree

4 Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated

5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice If jaundice develops, the medication should be discontinued

6 Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function

7 Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency

8 Serum folate levels may be depressed

9 The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted

10 Certain endocrine and liver function tests and blood components may be affected

(a) Increased sulfobromophthalein retention (b) Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone (d) Decreased pregnanediol excretion (e) Reduced response to metyrapone test

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage; hypertension, gallbladder disease, benign hepatomas, congenital anomalies

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed. mesenteric thrombosis neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related nausea and/or vomiting usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle Other reactions, as a general rule, are seen much less freguently or only occasionally gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma, breast changes, change in weight, change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature, intolerance to contact lenses

The following adverse reactions have been reported and the association has been neither confirmed nor refuted premenstrual-like syndrome, cataracts, changes in libido; chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication

After several months on treatment, bleeding may be reduced to a point of virtual absence, reduced flow may be a result of medication and not indicative of pregnancy

HOW SUPPLIED

Norlestrin $\boxed{21}$ 1/50 is available in compacts each containing 21 tablets Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{21}$ 2 5/50 is available in compacts each containing 21 tablets Each tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{Fe}$ 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{FE}$ 2 5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets Each pink tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{28}$ 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

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North Carolina Medical Journal

Features for Patients May 1985

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Updated 1985 by Donald McCollum, M.D.

My long term friend and neighbor, Mrs. Alice Cleland, became a candidate for hip surgery. I wheeled her to her room and noticed that she was holding a booklet telling her what to expect. She said that this was the single most helpful piece of paper ever given to her by a doctor. We are publishing the document. I hope it will inspire each of our readers to feed us information that is useful in patient care. All of you have useful tricks up your sleeves. The *Journal* is a good medium for sharing them with your colleagues.

E.A.S.

SO YOU ARE GOING TO HAVE A
TOTAL HIP REPLACEMENT...

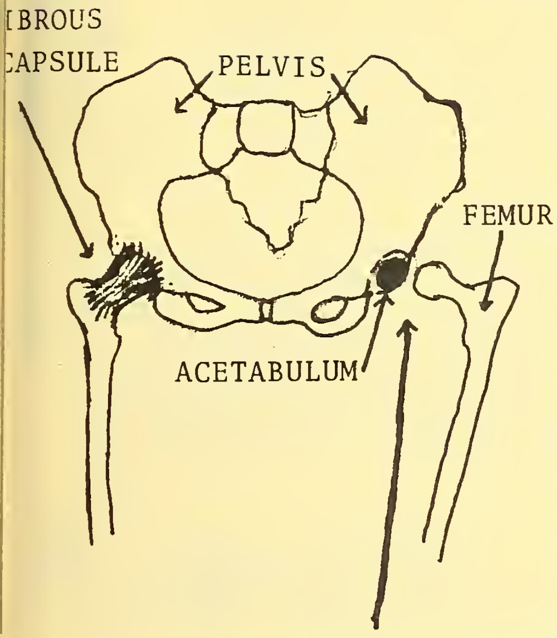
THIS BOOKLET IS PROVIDED TO HELP ANSWER SOME QUESTIONS YOU MIGHT HAVE ABOUT YOUR SURGERY AND TO GIVE YOU THE INFORMATION WHICH YOU'LL NEED TO MAKE THE QUICKEST POSSIBLE RECOVERY.

MEET MRS. SMITH

SHE BEGAN SEEING HER DOCTOR SEVERAL YEARS AGO FOR INCREASING PAIN IN HER HIP. SHE WAS GETTING NO RELIEF FROM MILD ANALGESICS AND WAS HAVING TROUBLE SLEEPING. FINDING NO INFECTION, HER DOCTOR SUGGESTED THAT SHE CONSIDER A TOTAL HIP REPLACEMENT.

A TOTAL HIP REPLACEMENT IS AN OPERATION WHERE THE DISEASED HIP JOINT IS REMOVED AND REPLACED BY AN ARTIFICIAL ONE.

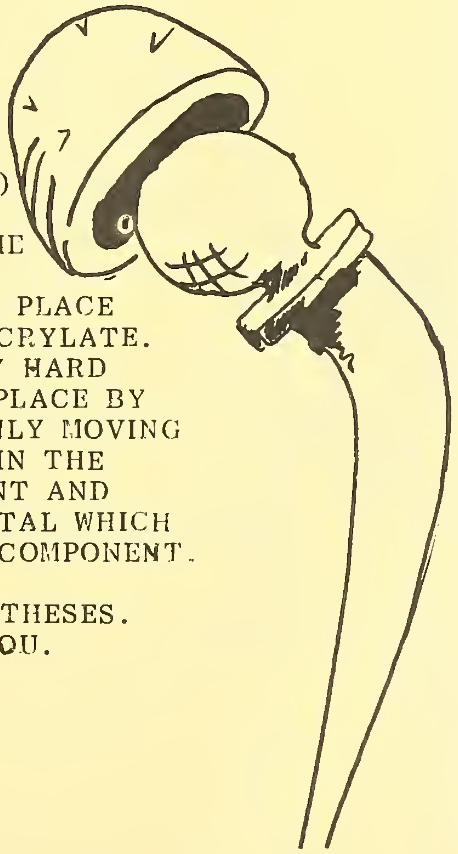
GEE, I DON'T KNOW ANYTHING...



THE NORMAL HUMAN HIP IS A "BALL AND SOCKET" JOINT. THE "BALL" IS THE HEAD OF THE FEMUR (THE LONG BONE OF THE THIGH), AND THE "SOCKET" IS A CUP-SHAPED AREA OF THE PELVIS CALLED THE ACETABULUM. THE INSIDE OF THE ACETABULUM AND THE HEAD OF THE FEMUR ARE COVERED WITH A GRISTLE-LIKE CARTILAGE WHICH PROVIDES A CUSHION FOR THE BONES AS WELL AS A SMOOTH, GLIDING SURFACE WHERE THEY MOVE AGAINST EACH OTHER. THE JOINT IS LUBRICATED WITH SYNOVIAL FLUID WHICH IS CONTAINED WITHIN THE JOINT CAPSULE. THE JOINT CAPSULE IS THE OUTER COVERING OF THE JOINT, AND IT IS MADE UP OF TOUGH FIBERS CALLED LIGAMENTS. THESE FIBERS HOLD THE BALL OF THE HIP JOINT IN THE SOCKET. .

HIP JOINT (OPENED)

ABOUT THE PROSTHESIS



E ARTIFICIAL JOINT IS CALLED A PROSTHESIS (PROS-TEA'-SIS)
D IT CONSISTS OF TWO PARTS. ONE PART, THE FEMORAL
MPONENT, IS MADE OF METAL AND REPLACES THE HEAD OF THE
IUR OR "BALL" PART OF THE JOINT. THE LONG STEM FITS
TO THE HOLLOW SHAFT OF THE FEMUR AND IS CEMENTED INTO PLACE
A SPECIAL ACRYLIC BONDING AGENT CALLED METHYL METHACRYLATE.
E "CUP" PART OF THE PROSTHESIS IS MADE OF AN EXTREMELY HARD
ASTIC CALLED POLYETHYLENE, AND IS ALSO CEMENTED INTO PLACE BY
THYL METHACRYLATE. AFTER THE CEMENT HARDENS, THE ONLY MOVING
RT OF THE ARTIFICIAL HIP JOINT IS THE INERT METAL BALL IN THE
ASTIC SOCKET. SEVERAL HIP PROSTHESES DO NOT USE CEMENT AND
E HELD IN PLACE BY BONY INGROWTH INTO PORES OF THE METAL WHICH
VERS THE CUP AND THE METAL WHICH COVERS THE FEMORAL COMPONENT.

ERE ARE SEVERAL DIFFERENT MODELS AND SIZES OF HIP PROSTHESES.
UR DOCTOR WILL CHOOSE THE ONE HE THINKS IS BEST FOR YOU.

WHEN DO I GO TO THE HOSPITAL?

YOU WILL PROBABLY ENTER THE HOSPITAL ONE DAY BEFORE YOUR SURGERY HAS BEEN SCHEDULED TO ALLOW TIME FOR TESTS AND PREPARATION. THIS WILL BE A BUSY TIME. YOUR MEDICAL HISTORY WILL BE TAKEN, AND YOU WILL BE GIVEN A PHYSICAL EXAMINATION. OTHER TESTS WILL EITHER BE DONE IN THE CLINIC OR LATER WHEN YOU ARRIVE IN YOUR ROOM ON THE WARD.

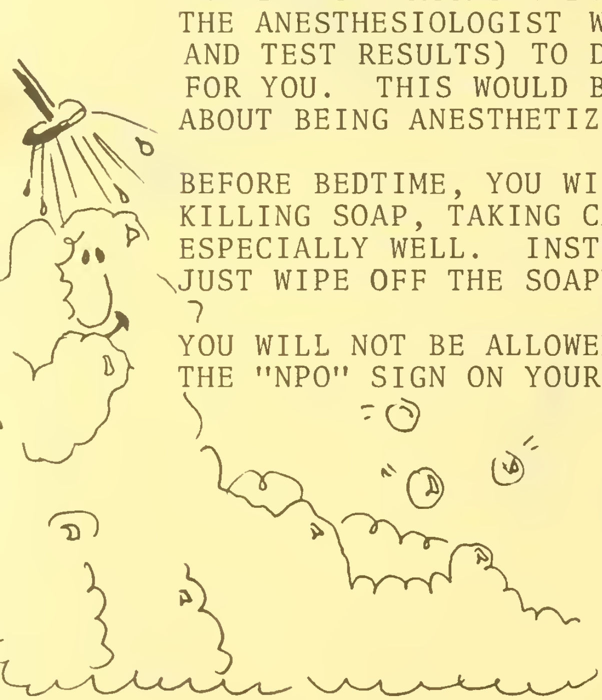
THE NURSE WILL ASK YOU TO PROVIDE A URINE SAMPLE AND EXPLAIN THE PROPER WAY TO OBTAIN THE SPECIMEN. BLOOD SAMPLES WILL BE DRAWN BY A LAB TECHNICIAN, SO THAT IT CAN BE TESTED AND CROSS-MATCHED IN THE BLOOD BANK. SINCE IT ISN'T UNUSUAL FOR A TRANSFUSION TO BE DONE DURING SURGERY, THE DOCTOR LIKES TO HAVE SEVERAL UNITS OF YOUR TYPE OF BLOOD ON HAND. IN ADDITION, A CHEST X-RAY AND AN EKG (ELECTROCARDIOGRAM) WILL BE PERFORMED. MOST OF THESE TESTS WILL BE DONE ON THE DAY OF ADMISSION, BUT IF THE DOCTOR SHOULD ORDER ANY ADDITIONAL ONES, THEY WILL BE MADE THE FOLLOWING DAY. FOR EXAMPLE, DEPENDING UPON YOUR AGE AND GENERAL CONDITION, THE DOCTOR MAY ORDER A CONSULTATION WITH A CARDIOLOGIST TO GATHER FURTHER INFORMATION SO THAT YOU WILL BE RECEIVING VERY PERSONALIZED CARE.

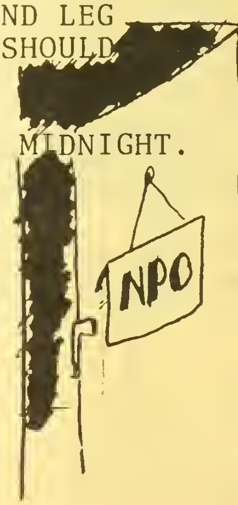
TO MAKE THE TESTING PROCEDURES GO SMOOTHLY, IT IS BEST THAT YOU WEAR A HOSPITAL GOWN AND THAT YOU DO NOT LEAVE THE WARD WITHOUT ASKING THE CHARGE NURSE.

THE DOCTOR WILL WANT TO TALK WITH YOU ABOUT YOUR SURGERY, ANSWER ANY QUESTIONS YOU MIGHT HAVE, AND THEN HAVE YOU SIGN A PERMIT FORM AUTHORIZING THE SURGEON TO PERFORM THE OPERATION. THE ANESTHESIOLOGIST WILL VISIT (AFTER LOOKING AT YOUR CHART AND TEST RESULTS) TO DISCUSS WHICH TYPE OF ANESTHESIA IS BEST FOR YOU. THIS WOULD BE AN IDEAL TIME TO ASK HIM ANY QUESTIONS ABOUT BEING ANESTHETIZED.

BEFORE BEDTIME, YOU WILL NEED TO SHOWER WITH A SPECIAL GERM-KILLING SOAP, TAKING CARE TO SCRUB YOUR HIP, PELVIS, AND LEG ESPECIALLY WELL. INSTEAD OF RINSING OFF THE SOAP YOU SHOULD JUST WIPE OFF THE SOAPY SOLUTION WITH A CLEAN TOWEL.

YOU WILL NOT BE ALLOWED ANYTHING TO EAT OR DRINK AFTER MIDNIGHT. THE "NPO" SIGN ON YOUR DOOR MEANS "NOTHING BY MOUTH."





EARLY THE NEXT MORNING...

EARLY THE NEXT MORNING, THE NURSE WILL WAKE YOU AND ASK YOU TO BATHE AGAIN WITH THE GERM-KILLING SOAP. SOON A NURSE FROM THE OPERATING ROOM WILL COME BY AND SHAVE YOUR LEG AND HIP COMPLETELY. SUCH THOROUGH CLEANSING IS NECESSARY FOR PROTECTING YOU AGAINST INFECTION.

YOU WILL BE GIVEN A HOSPITAL GOWN TO WEAR AND ASKED TO REMOVE ANY OTHER CLOTHES. JEWELRY, MONEY, OR OTHER VALUABLES CAN BE LOCKED UP BY THE NURSE IF YOUR FAMILY CANNOT KEEP THEM FOR YOU. IF YOU WEAR FALSE TEETH, CONTACT LENSES, OR OTHER PROSTHESES, THEY NEED TO BE SAFELY STORED IN YOUR ROOM SO THAT THEY WILL BE PROPERLY CARED FOR AND NOT LOST. NAIL POLISH MUST BE REMOVED SO THAT THE ANESTHESIOLOGIST CAN CHECK YOUR CIRCULATION DURING THE OPERATION.

AM I READY YET?

NOW YOU ARE READY TO BE TAKEN TO THE OPERATING ROOM. THE NURSE WILL HELP YOU TO THE BATHROOM TO EMPTY YOUR BLADDER BEFORE YOU LEAVE. SHE WILL THEN GIVE YOU SOME MEDICINE TO HELP YOU RELAX AND TO DRY UP THE SECRETIONS IN YOUR LUNGS. THIS WILL HELP EASE YOUR BREATHING WHILE YOU ARE ASLEEP, ALTHOUGH IT MAY MAKE YOUR MOUTH FEEL DRY.

A NURSE FROM THE WARD WILL ACCOMPANY YOU AS YOU ARE MOVED IN YOUR OWN BED TO THE ENTRANCE OF THE OPERATING ROOMS. THERE, THE O. R. NURSE WILL CHECK YOU IN BEFORE YOU PROCEED A SHORT DISTANCE TO THE PRE-ANESTHESIA ROOM. YOUR ANESTHETIST WILL MEET YOU TO CHECK YOUR PULSE, BLOOD PRESSURE, AND TO START AN I.V. THE I.V. IS A SMALL TUBE WHICH CARRIES FLUIDS AND MEDICATION INTO A VEIN IN YOUR ARM. AFTER THE I.V. IS IN PLACE, YOU SHOULD SOON FEEL DROWSY AND FALL ASLEEP.

THE OPERATION

THE DOCTOR WILL PROBABLY USE A 7 TO 9 INCH INCISION ALONG THE SIDE OF YOUR HIP. HE WILL THEN LOCATE THE TOUGH CAPSULE OF THE JOINT UNDER THE SURROUNDING MUSCLES. THE CAPSULE IS OPENED, EXPOSING THE INSIDE OF THE JOINT. THE DOCTOR NEXT REMOVES THE HEAD OF THE FEMUR (OR "BALL" PART OF THE JOINT).

NEXT, THE DOCTOR ENLARGES YOUR ACETABULUM ("SOCKET" PART OF THE JOINT) JUST ENOUGH TO HOLD THE ACETABULAR COMPONENT OF THE PROSTHESIS. BOTH COMPONENTS ARE THEN PUT INTO PLACE AND TESTED FOR A PROPER FIT. ONCE THE DOCTOR IS SATISFIED WITH THESE RESULTS, HE CEMENTS BOTH COMPONENTS INTO PLACE AND SUTURES THE WOUND CLOSED. THE OPERATION IS OVER!

THE SURGERY ITSELF TAKES ONLY FROM 1 1/2 TO 3 HOURS, BUT YOUR FAMILY CAN EXPECT YOU TO BE AWAY FROM YOUR ROOM FOR 4 TO 7 HOURS TOTAL. SPECIAL SKIN PREPARATION IN THE OPERATING ROOM TAKES AT LEAST 1/2 HOUR AFTER YOU ARE PUT TO SLEEP! MOST PATIENTS SPEND AT LEAST 2 HOURS IN THE RECOVERY ROOM AFTER SURGERY, BUT IT IS NOT UNUSUAL TO REMAIN THERE FOR AN EVEN LONGER PERIOD OF TIME. YOU WILL BE ABLE TO RETURN TO THE WARD AS SOON AS YOUR DOCTOR FEELS IT IS SAFE TO DO SO.

THE RECOVERY ROOM

YOU WILL BE TAKEN IN YOUR OWN BED TO THE RECOVERY ROOM AFTER SURGERY IS FINISHED. YOU WILL BE PARTIALLY AWAKE BY THIS TIME, BUT YOU WILL STILL FEEL VERY DROWSY. YOUR OWN SPECIAL NURSE WILL STAY WITH YOU AT ALL TIMES, CHECKING YOUR PULSE AND BLOOD PRESSURE FREQUENTLY AS SHE KEEPS CAREFUL WATCH OVER YOUR CONDITION. SHE WILL BE REMINDING YOU TO BREATHE DEEPLY AND TO COUGH SO THAT YOU WILL AWAKEN MORE QUICKLY.

DEEP BREATHING & COUGHING

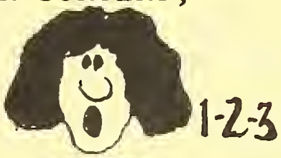
YOUR LUNGS NORMALLY SECRETE FLUID CONSTANTLY, TO KEEP THE LUNGS MOIST. WHEN YOU ARE IN GOOD HEALTH, THIS CAUSES NO PROBLEMS BECAUSE TINY HAIRS IN YOUR AIRWAYS BRING THE FLUID UP TO THE THROAT AND YOU SWALLOW IT UNCONSCIOUSLY. WHEN YOU ARE PUT TO SLEEP, THE ANESTHESIA SLOWS THE BODY'S MEANS OF BRINGING UP THE FLUID. IF GASSES ARE USED, THEY CAN IRRITATE THE LUNGS SLIGHTLY AND FURTHER INCREASE THE SECRETIONS. THEREFORE, WHEN YOU AWAKEN, THERE IS SOME FLUID IN YOUR LUNGS WHICH WILL REQUIRE COUGHING TO BRING IT UP.

DEEP BREATHING BEFORE COUGHING HELPS TO LOOSEN THIS FLUID AND OPEN UP YOUR LUNGS FOR A GOOD, DEEP COUGH.

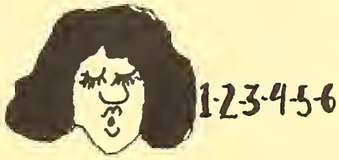
YOUR NURSE WILL BE REMINDING YOU OFTEN TO BREATHE DEEPLY AND COUGH!!!

IN ORDER TO DEEP BREATHE AND TO COUGH PROPERLY AFTER SURGERY, IT IS A GOOD IDEA TO PRACTICE THE NIGHT BEFORE.

1. TAKE IN A DEEP BREATH WITH YOUR MOUTH OPEN TO THE COUNT OF 3.



2. PUCKER YOUR LIPS AND BLOW OUT TO THE COUNT OF 6.

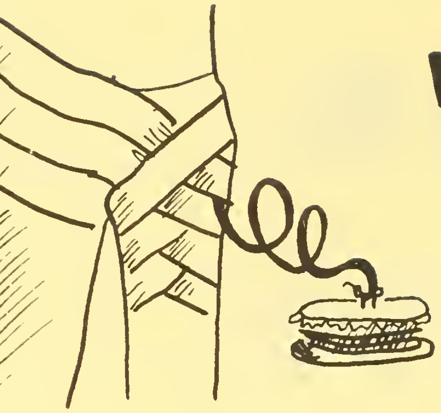


3. DO A DEEP DOUBLE COUGH. . ("ahem. . .AHEM")

YOUR ABDOMEN (BELLY AREA) SHOULD MOVE UP AND DOWN WITH EACH DEEP BREATH AND COUGH. THIS ASSURES YOU THAT YOU ARE DOING IT CORRECTLY.

IF THIS FLUID IS NOT COUGHED UP, THE COLLECTION OF FLUID IN YOUR LUNGS COULD CAUSE PNEUMONIA. NOTHING IS MORE EFFECTIVE IN PREVENTING THE ONSET OF PNEUMONIA THAN DEEP BREATHING AND COUGHING.

THIS IS ONE POSITIVE STEP IN SPEEDING YOUR RECOVERY THAT ONLY YOU CAN TAKE!!!



WHAT ABOUT MY HIP?

YOUR HIP WILL BE WRAPPED WITH A SOFT DRESSING WHICH WILL STAY IN PLACE FOR ABOUT FIVE DAYS. AFTER THE DRESSING IS REMOVED, YOUR INCISION WILL BE COVERED WITH A LARGE BANDAID. TEN DAYS AFTER SURGERY WHEN THE WOUND IS HEALED, THE STITCHES OR SKIN CLIPS WILL BE REMOVED.

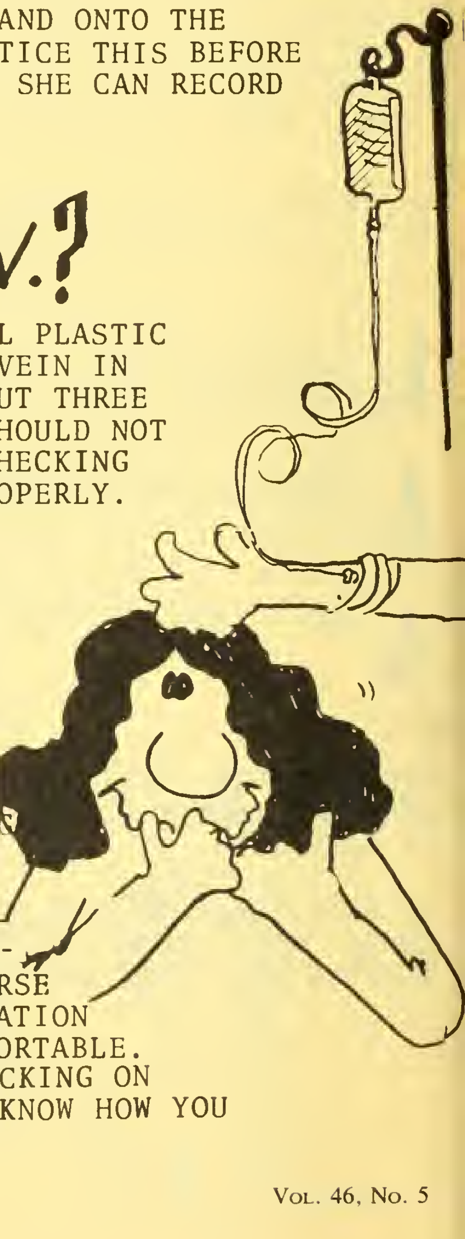
WHEN YOU AWAKEN FROM SURGERY A PLASTIC TUBING WILL BE NOTICEABLE COMING FROM BENEATH YOUR DRESSING AND ATTACHING TO A SMALL COMPRESSIBLE CONTAINER. THIS IS A DRAIN CALLED A "HEMOVAC" AND IT LEADS TO YOUR INCISION. THE HEMOVAC ALLOWS ANY DRAINAGE IN YOUR WOUND TO RUN OFF AND PREVENTS A PAINFUL SWELLING CALLED A HEMATOMA TO FORM INSIDE YOUR INCISION SITE. THE HEMOVAC WILL BE REMOVED AFTER ALL DRAINAGE HAS STOPPED (ABOUT TWO DAYS). OCCASIONALLY, DRAINAGE WILL SEEP FROM AROUND THE HEMOVAC AND ONTO THE DRESSING. DO NOT BE ALARMED, BUT IF YOU NOTICE THIS BEFORE THE NURSE DOES, BE SURE TO TELL HER SO THAT SHE CAN RECORD THE AMOUNT AND KEEP YOUR DRESSING DRY.

WILL I STILL HAVE AN I.V.?

AS WAS MENTIONED BEFORE, THE I.V. IS A SMALL PLASTIC TUBE THAT CARRIES FLUID AND MEDICINES TO A VEIN IN ONE OF YOUR ARMS. YOU WILL NEED IT FOR ABOUT THREE DAYS TO RECEIVE THESE MEDICATIONS, BUT IT SHOULD NOT CAUSE ANY DISCOMFORT. THE NURSES WILL BE CHECKING IT FREQUENTLY TO MAKE SURE IT IS RUNNING PROPERLY.

WILL THIS BE PAINFUL?

SOME PAIN AND SORENESS IS EXPECTED FOLLOWING HIP SURGERY, BUT YOUR DOCTOR WILL HAVE ORDERED MEDICATION IF YOU SHOULD HAPPEN TO NEED IT. AFTER ABOUT TWO DAYS, REGULAR ASPIRIN SHOULD BE ALL THAT YOU NEED FOR COMFORT. IT IS IMPORTANT THAT YOU TELL THE NURSE AS SOON AS YOU FEEL THE NEED FOR PAIN MEDICATION AND NOT WAIT UNTIL YOU ARE EXTREMELY UNCOMFORTABLE. REMEMBER THAT EVEN THOUGH YOUR NURSE IS CHECKING ON YOU FREQUENTLY, IT IS UP TO YOU TO LET HER KNOW HOW YOU ARE FEELING.



DO I STAY IN BED FOR LONG?

FOR THE FIRST DAY AFTER YOUR SURGERY, YOU WILL NEED TO REMAIN IN BED. ABOUT THE SECOND OR THIRD DAY YOU WILL BE ALLOWED UP IN A CHAIR AND THEN AFTER THAT YOU WILL BEGIN WALKING WITH HELP FROM PHYSICAL THERAPY.

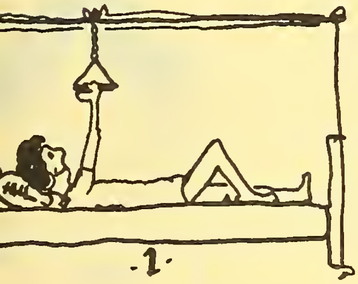
FREQUENT CHANGE OF POSITION HELPS TO CLEAR THE FLUID FROM YOUR LUNGS, IMPROVES YOUR CIRCULATION, AND MAKES YOU MORE COMFORTABLE.

HOW WILL I MOVE?

TO HELP YOU MOVE IN BED AFTER SURGERY, YOUR BED WILL BE EQUIPPED WITH AN OVERHEAD FRAME WHICH SUPPORTS A "TRAPEZE BAR." BY USING YOUR ARMS, YOU CAN MOVE AROUND MORE EASILY. PRACTICING WITH THE TRAPEZE BEFORE SURGERY WILL GIVE YOU THE FEEL OF THE MANEUVER AND WILL BE GOOD PREPARATION FOR USING IT LATER.

IT'S EASY!

HERE'S HOW...



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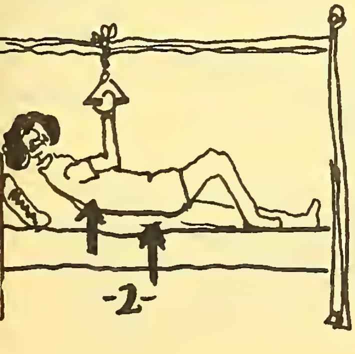

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IF YOU ARE LYING ON YOUR BACK, JUST BEND YOUR "GOOD" LEG UP KEEPING THE SOLE OF YOUR FOOT FLAT ON THE BED.

REACH UP AND GRAB THE TRAPEZE BAR WITH ONE OR BOTH HANDS.

THEN, BY PULLING ON THE TRAPEZE BAR AND PUSHING DOWN WITH THE LEG THAT IS BENT, YOU CAN LIFT YOUR BODY FROM THE BED AND MOVE IT IN ANY DIRECTION.

WON'T IT BE DANGEROUS TO TURN ON MY HIP?

NO! ACTUALLY, YOUR NEW HIP IS SAFEST WHEN YOU ARE LYING ON IT!!! THIS POSITION AIDS DRAINAGE AND PREVENTS DISLOCATION OF THE JOINT. THE ONLY DANGEROUS POSITION FOR YOU EXISTS WHEN YOU ADDUCT YOUR OPERATIVE LEG. (THAT IS, WHEN YOU MOVE THAT LEG IN TOWARD THE OTHER ONE.) BEFORE YOUR HIP HAS HEALED, IT IS POSSIBLE THAT ADDUCTING YOUR LEG MAY CAUSE DISLOCATION OF THE PROSTHESIS.

BUT REMEMBER...

1. DO NOT ALLOW YOUR OPERATIVE LEG TO SWING INWARD! TRY TO KEEP YOUR LEGS SLIGHTLY APART AT ALL TIMES, PLACING A PILLOW BETWEEN THEM IF NECESSARY.

2. KEEP YOUR FEET AS HIGH AS YOUR KNEES AND HIGHER THAN THE LEVEL OF YOUR HEART WHEN YOU ARE LYING ON YOUR BACK.

3. NEVER CROSS YOUR LEGS.

4. DO NOT TURN ONTO YOUR NON-OPERATIVE SIDE WITHOUT HELP FROM A NURSE. SHE WILL NEED TO SPECIALLY POSITION YOU WITH PILLOWS BEFORE YOU TURN SO THAT DISLOCATION WILL NOT OCCUR.

5. TRY TO KEEP YOUR KNEE CAPS AND TOES POINTED TOWARD THE CEILING WHEN YOU ARE LYING ON YOUR BACK.

BY THE TIME YOU LEAVE THE HOSPITAL, YOU SHOULD BE ABLE TO TURN TO EITHER SIDE SAFELY, BUT YOU SHOULD AVOID CROSSING YOUR LEGS FOR SEVERAL WEEKS.

I'VE HEARD OF BLOOD CLOTS. . .

BLOOD CLOTS, OR THROMBI, IN THE LEGS ARE A DANGER TO EVERY PATIENT AFTER SURGERY. IF A CLOT SHOULD HAPPEN TO FORM IN THE LEGS, IT COULD BREAK LOOSE AND TRAVEL TO THE LUNGS, CAUSING SERIOUS ILLNESS. ALTHOUGH THIS RARELY OCCURS, EVERY PRECAUTION IS TAKEN TO PREVENT CLOTS FROM FORMING. PART OF YOUR MEDICATION AFTER SURGERY WILL "THIN" YOUR BLOOD SLIGHTLY TO PREVENT CLOT FORMATION. YOU WILL BE GIVEN SPECIAL STOCKINGS TO WEAR AFTER SURGERY AND ASKED TO KEEP YOUR FEET HIGHER THAN HEART LEVEL WHILE LYING IN BED. MOST IMPORTANT, YOU WILL BE DOING SOME EXERCISES TO KEEP YOUR BLOOD CIRCULATING SO THAT CLOTS DON'T HAVE THE CHANCE TO FORM.

ID YOU SAY EXERCISES?

EXERCISING IS VERY IMPORTANT AFTER SURGERY. IT IS A MUST FOR MAINTAINING GOOD CIRCUALTION AND MUSCLE TONE IN YOUR LEGS AND ARMS.

THE FOLLOWING EXERCISES MAY BE BEGUN BEFORE SURGERY. AFTER SURGERY, THEY SHOULD BE DONE AT LEAST FIVE TIMES DURING EACH HOUR THAT YOU ARE AWAKE, UNLESS YOU ARE GIVEN DIFFERENT INSTRUCTIONS.
HOLD EACH OF THE FOLLOWING FOR A SLOW COUNT OF FIVE.

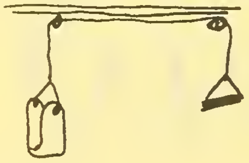
1. CURL AND WIGGLE TOES.
2. MOVE ANKLES UP AND DOWN AND AROUND IN CIRCLES.
3. TIGHTEN KNEES BY STIFFENING YOUR FRONT THIGH MUSCLES.
4. TIGHTEN THE BUTTOCKS MUSCLES WITH KNEES KEPT STRAIGHT.
5. TAKE A DEEP BREATH, FILLING THE LUNGS, THEN LET AIR OUT SLOWLY. COUGH DEEPLY.
6. USING TRAPEZE BAR AND NON-OPERATIVE LEG, LIFT YOUR TRUNK OFF THE BED KEEPING YOUR HIPS STRAIGHT. (DO THIS WHILE LYING ON YOUR BACK.)

YOUR DOCTORS MAY FEEL THAT YOU SHOULD BEGIN EXERCISES (NUMBERS 1 THROUGH 4) SEVERAL WEEKS BEFORE SURGERY. YOUR MUSCLES WILL BE STRENGTHENED SO THAT YOU WILL ARRIVE FOR SURGERY IN THE BEST POSSIBLE CONDITION AND INCREASE THE SPEED AND EASE OF YOUR RECOVERY.

IS THIS THE PHYSICAL THERAPIST?

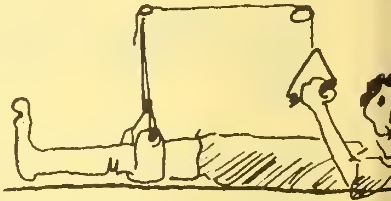
THE PHYSICAL THERAPIST WILL HELP YOU WITH YOUR MORE ADVANCED EXERCISES AFTER SURGERY. THEY ARE USUALLY BEGUN ON THE FOURTH OR FIFTH DAY FOLLOWING THE OPERATION.

IN ADDITION TO YOUR TRAPEZE BAR, A SLING IS SUSPENDED FROM THE FRAME OVER YOUR BED BY A SYSTEM OF PULLEYS. THE FOLLOWING EXERCISES USING THE SLING WILL BE STARTED 4-5 DAYS AFTER YOUR SURGERY WITH HELP FROM YOUR PHYSICAL THERAPIST. THEY ARE TO BE DONE USING YOUR LEG MUSCLES AS MUCH AS POSSIBLE. YOU SHOULD RELY ON THE USE OF THE SLING ONLY WHEN ABSOLUTELY NECESSARY. BEGIN BY DOING THE NUMBER OF EXERCISES AS YOU ARE INSTRUCTED AND ADD 1 REPETITION EACH TIME YOU DO THEM.



KNEE TO CHEST

→ 1. LIE ON YOUR BACK WITH YOUR LEGS OUT STRAIGHT. PLACE THE PULLEY PAD UNDER YOUR THIGH.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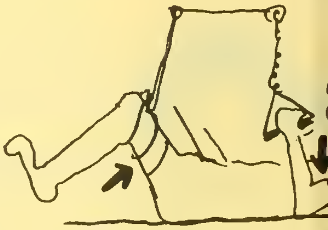
→ 2. BEND YOUR KNEE, RAISING IT UP TOWARD YOUR CHEST. RAISE IT AS FAR AS YOU CAN WITHOUT USING THE PULLEY. THEN, BY PULLING STRAIGHT DOWN ON THE PULLEY, YOU CAN RAISE YOUR LEG FURTHER UP TOWARD YOUR CHEST. YOU WILL HAVE TO WORK THROUGH SOME PAIN, BUT DO NOT FORCE YOUR LEG BEYOND REASON.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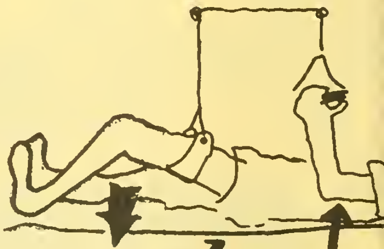
→ 3. THEN LOWER YOUR LEG BACK TO THE STARTING POSITION #1 BY STRAIGHTENING YOUR KNEE AND RELEASING THE PULLEY GRADUALLY.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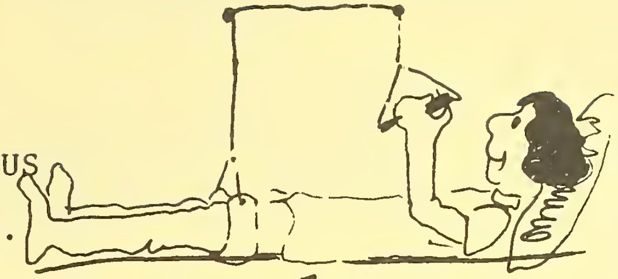
STRAIGHT LEG



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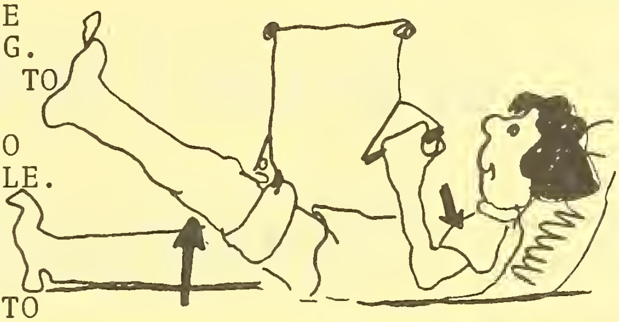
1. BEGIN IN SAME POSITION AS PREVIOUS EXERCISE---ON YOUR BACK, LEGS STRAIGHT, PULLEY PAD UNDER THIGH.

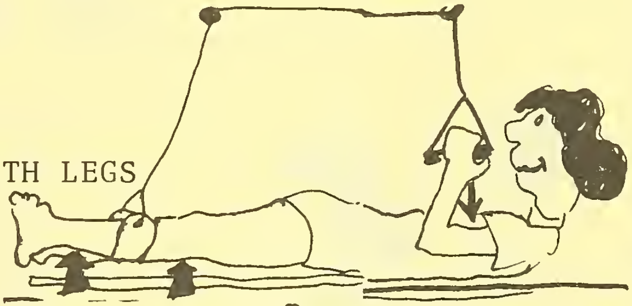


2

2. KEEPING YOUR KNEE STRAIGHT, RAISE YOUR ENTIRE LEG UP TOWARD CEILING. YOU WILL PROBABLY NEED THE SLING TO HELP YOU, BUT YOU SHOULD CONCENTRATE ON USING THE LEG MUSCLES TO RAISE YOUR LEG AS MUCH AS POSSIBLE.

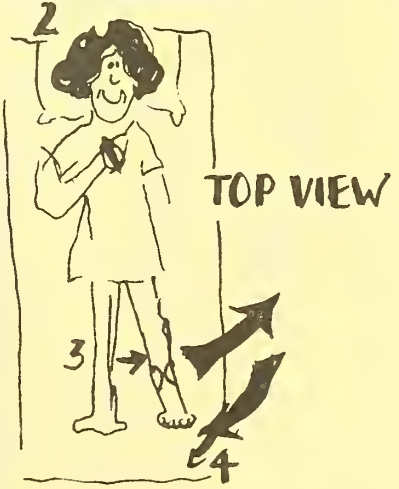
3. THEN SLOWLY LOWER YOUR LEG BACK TO STARTING POSITION #1 BY GRADUALLY RELEASING THE PULLEY AND CONTROLLING YOUR LEG AS IT GOES BACK DOWN.

LEG TO SIDE



1. LIE ON YOUR BACK AS BEFORE WITH LEGS STRAIGHT AND SLING UNDER YOUR CALF.

2. KEEPING YOUR KNEE STRAIGHT, PULL DOWN ON PULLEY HANDLE LIFTING YOUR LEG UP JUST ENOUGH FOR THE HEEL TO BARELY CLEAR THE BED---NO FURTHER!



3. THEN MOVE YOUR LEG OUT TO THE SIDE, KEEPING YOUR KNEE STRAIGHT AND POINTING UP TOWARD THE CEILING.

4. THEN BRING LEG BACK IN TOWARD THE CENTER.

WHEW! SOUNDS TIRING! WHY SHOULD I?

THE BENEFITS THAT YOU RECEIVE FROM YOUR NEW HIP JOINT WILL DEPEND LARGELY ON YOU! YOU MUST EXERCISE FAITHFULLY AND CORRECTLY, FOLLOWING INSTRUCTIONS FROM YOUR DOCTOR AND THERAPIST TO THE LETTER! AT THIS POINT YOU BECOME THE KEY TO A SUCCESSFUL RECOVERY AND A HAPPY LIFE WITH YOUR NEW HIP.

WHEN CAN I BE OUT OF BED?

MANY PATIENTS ARE ABLE TO BE OUT OF BED IN A CHAIR FOR SHORT PERIODS OF TIME AS EARLY AS THE SECOND OR THIRD DAY.

CAN I WALK AGAIN SOON?

BY THE FIFTH DAY OR SO, YOU WILL PROBABLY BEGIN WALKING WITH HELP FROM THE PHYSICAL THERAPY DEPARTMENT. SINCE YOU WILL NEED TO USE A WALKER OR CRUTCHES FOR SOME TIME AT HOME, IT IS IMPORTANT TO LEARN TO USE THEM WELL WHILE YOU ARE IN THE HOSPITAL.

PAY STRICT ATTENTION TO THE THERAPIST'S INSTRUCTIONS AND TAKE CARE NOT TO PLACE ANY MORE WEIGHT ON YOUR NEW HIP THAN YOU ARE INSTRUCTED.

DO I TAKE SPECIAL CARE AT HOME?

WITHIN A FEW MONTHS AFTER YOU LEAVE THE HOSPITAL, YOU SHOULD BE REGAINING FULL USE OF YOUR NEW HIP. GENERALLY, IF YOU ARE TAKING GOOD CARE OF YOURSELF, YOUR HIP WILL NOT REQUIRE ANY SPECIAL ATTENTION.

ANY PRECAUTIONS?

THE ONLY REAL PRECAUTION YOU WILL NEED TO TAKE CONCERNS INFECTIONS. BACTERIA WHICH NORMALLY CAUSE NO PROBLEMS IN YOUR BODY SOMETIMES DO CAUSE PROBLEMS IN A NEW HIP BECAUSE THERE IS NO BLOOD SUPPLY IN THE ARTIFICIAL JOINT TO FIGHT BACTERIA.

THEREFORE, IF YOU ARE TO BE TREATED BY ANY OTHER DOCTORS OR DENTISTS, IT IS IMPORTANT TO INFORM THEM ABOUT YOUR HIP, IN CASE IT WOULD BE NECESSARY FOR THEM TO PROTECT YOU WITH ANTIBIOTICS.

AFTER ANY SURGERY THE MOUTH OR RECTUM REQUIRES SPECIAL CAUTION. IF YOU HAVE YOUR TEETH CLEANED AND SCALED, YOU SHOULD TAKE ANTIBIOTICS ONE HOUR BEFORE AND SIX HOURS AFTER THE PROCEDURE.

AND. . . IF YOU SHOULD NOTICE ANY EXCESSIVE PAIN, SWELLING OR REDNESS IN YOUR HIP JOINT,

CALL HIM IMMEDIATELY!

BY EXPRESSING HER NEEDS AND CONCERNS WITH THE HEALTH CARE TEAM AND CAREFULLY FOLLOWING THEIR INSTRUCTIONS, MRS. SMITH EXPERIENCED A RAPID RECOVERY FROM SURGERY. SHE HAS NOW RETURNED TO HER PREVIOUS ACTIVITIES AND IS ENJOYING LIFE WITH HER TOTAL HIP REPLACEMENT!

HER CONVERSATIONS WITH THE SURGEON, THE NURSES, AND THERAPIST ANSWERED ALL OF HER QUESTIONS AND PERHAPS SEVERAL OF YOURS.

BY WORKING TOGETHER, WE CAN BEST ACHIEVE OUR GOALS FOR YOU. . . A SPEEDY RECOVERY AND MANY HAPPY YEARS WITH YOUR

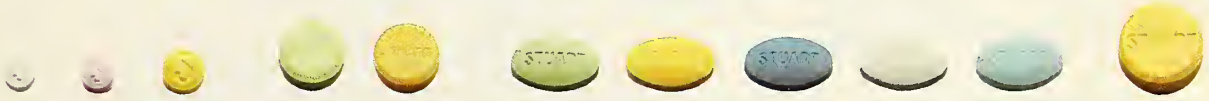
TOTAL HIP REPLACEMENT!

Angina comes in many forms...

So does SORBITRATE®

(ISOSORBIDE DINITRATE)

Unsurpassed flexibility in nitrate therapy.



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See following page for brief summary of prescribing information.

SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent Cutaneous vasodilation with flushing may occur Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined *The oral controlled-release forms of isosorbide dinitrate should not be chewed*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg)

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AIR FORCE

A great way of life

Dr. Joseph Willis Beard: A Mighty Man, 1902-1983

R. McIntyre Bridges, M.D.

FEW men have been so much to so many in so short a period of time. Dr. Beard's accomplishments as a pioneer virologist, a teaching surgeon, a dairy farmer, a philosopher and an admired genius will stand the test of time.

Joseph Willis Beard was born in Athens, Louisiana, in 1902, the eldest of two sons of Jasper Beard and Frazier Bridges. To know and understand the obsessive drive of this man requires that one know his early background and childhood. We must spend the time on Dr. Beard's parents in order to fully appreciate his desire to develop character and intellect, though these characteristics are poles apart. Intellect sufficeth not; character is also needed.

His father, Jasper, was a humble hardwood floor finisher. All of his work was by hand and on his knees. Sanding and varnishing hardwood floors produced knees of enormous size. To have seen them, one would have expressed amazement at his ability to work. Jasper's role was vital to the making of Joe Beard, since he saved with an obsession to educate Joe. Ida Bridges Hall, his wife's sister, found six thousand dollars in a coffee can; Jasper told her, "This is for Joe's education, and I will do all in my power to see that he is educated."

His mother, Frazier Beard, was the oldest of five sisters and two brothers, children of the Sophie and Wardlow Bridges family (figure 1). Like her mother, Sophie, Frazier assumed a matriarchal and domineering stance, which prohibited any emotional closeness.

To provide some insight into the Bridges girls, Hunter Bridges, oldest son of Sophie and Wardlow Bridges, bought a set of the Harvard Classics. Frazier's sisters saw them, declared them pornographic, and burned the set in the back yard!

No one ever doubted the courage of Joe Beard. As a child he was independent, and he would accept any physical challenge. At the age of thirteen he was forced to leave his home in Athens, Louisiana because of his inability to socialize with his peers. He was sent to Shreveport, Louisiana to live with his mother's family, the Bridges, who had moved to Shreveport in 1910. A drought had forced them to move to Travis Street across from Shreve Memorial Library.

Wardlow Bridges, his grandfather, had been a school teacher in Athens, Louisiana. Upon moving to Shreveport

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From 128 Homer Road, Minden, LA 71055-2799.

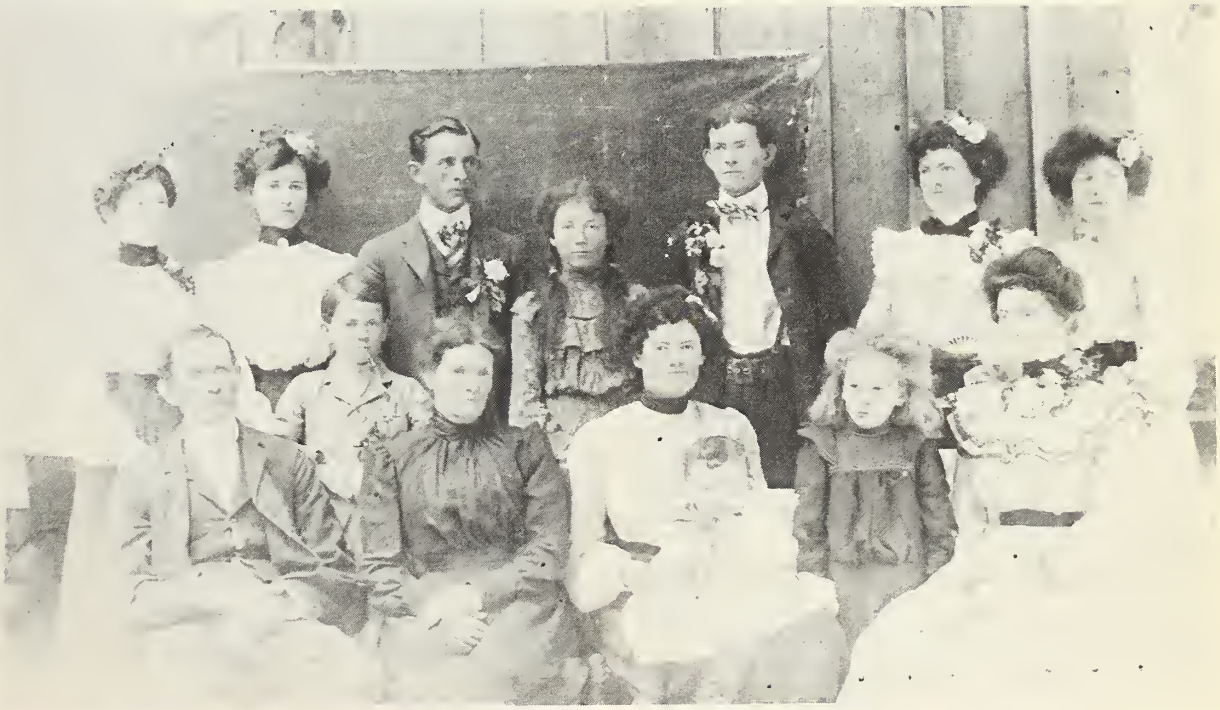


Figure 1. *Joe Beard as a baby sitting on his mother's lap in a photograph of the Bridges family.*

he became a night watchman at warehouses on the banks of the Red River. Each night Joe Beard would go to work with his grandfather, who taught him to read and who instilled in him the desire to learn. Having built-in courage, he now developed an intense desire for knowledge. These two traits he always considered the requirements for greatness.

A year and a half with the Bridges family ended because Joe Beard was unable to get along with the Bridges' youngest son, Murphy, and he was again forced to move. His parents moved from Athens to Shreveport and Joe registered at the Hope Street High School, across from the library, but found little success there. He spent his days in the Shreve Memorial Library. The librarian would pile books on his desk in the library and Joe became obsessed with the wisdom of Plato, Aristotle, Shakespeare and others. Yet he never graduated from high school.

At fifteen years of age a tragedy struck that left its scar on Joe for life. One day a friend and Joe went hunting. His mother insisted that Joe take his younger brother, Ross, along. At Seven Springs, a wooded area in Shreveport, the friend pointed his gun at Ross, which he thought was unloaded, trying to discourage his following them. A shotgun shell happened to be in the gun and, when triggered, exploded. Ross died five months later. Joe's mother, never expressing much love, blamed Joe, and provided him a life of misery after the death of Ross. At this point in Joe's life one must ask the question, "Did this motherly rejection contribute to his greatness?" His quest for knowledge through books became his world.

At the age of seventeen Joe divorced himself from his family and went to work clearing rights-of-way for roads and railroads around Shreveport. He fed his thirst for knowledge by reading anything he could obtain.

After three years on road gangs he presented himself to Centenary College, a private Methodist School in Shreveport, Louisiana. With no High School diploma, he talked his way past the admissions office. He obviously excelled. In 1922, he entered the University of Chicago. He graduated with a Bachelor of Science degree (figure 2), and applied and was accepted for medical school at Vanderbilt University. Shortly after entering Medical School he married Louise Conley, a fellow medical student. After obtaining his M.D. degree he interned and began his surgical residency. Two years into his surgical residency his first marriage ended in divorce.

Shortly afterward he married a nurse at Vanderbilt Hospital, Dorothy Waters (figure 3). This marriage was to endure to his death. Dorothy Beard's interests were inseparable from Dr. Joe Beard's interests and they worked together diligently.

At Vanderbilt, Al Blalock, a classmate, was a good friend of Dr. Beard. Dr. Beard had an ability to seek out those of intellect and attracted the same. Dr. Blalock became Department Head & Chief of Surgery at Johns Hopkins University Medical School.

One should clarify friendships of Dr. Joseph W. Beard: he avoided familiarities in relations with others. He was critical with a vengeance of those superficial with knowledge and of the ignorant who had the opportunity to be otherwise. As he once said, "The stars keep their brilliance by not making themselves common." One would derive

Figure 2. *Dr. Beard's graduation picture from the University of Chicago.*

Figure 3. *Dorothy Beard as a surgical nurse at Vanderbilt University Medical School.*

the impression that Joe Beard felt familiarity bordered on vulgarity. However, one knowing his childhood would gain the impression he feared being hurt.

While in his surgical residency he became interested in the brand new field of viral research and, finishing his residency, he went to Rockefeller Center to work with Peyton Rouse. Peyton Rouse was Dr. Beard's ruling star— as Joe Beard would say, "None so helpless as not to have one." Peyton Rouse and Dr. Beard were pioneers in viral research and attracted many men to the field.

In 1937, Joe joined the faculty of Duke University Medical School as a professor of experimental surgery and viral research (figure 4). In the words of Dr. Eugene Stead, Professor of Medicine and Head of the Department of Medicine, no other member of the faculty had more to do with changing Duke University Medical School from a regional institution to one of national and international recognition. His productivity as a viral scientist escalated through the years at Duke University Medical School.

Shortly after Dr. Beard joined the University staff, the survival of the whole thoroughbred horse population in Kentucky was threatened by equine encephalitis. With a grant from Lederle Laboratories, Dr. Beard developed a vaccine which prevented the death of thousands of horses nationwide. This outstanding achievement was to end in a personal tragedy.

At the insistence of representatives of Lederle Laboratories Dr. Beard patented the vaccine. His work resulted in the first successful vaccine effective against the virus of equine encephalitis. The discovery attracted national and international attention. Rumors were circulated that he was being considered for the Nobel Prize. When the existence of a patent was disclosed, even though all proceeds were designated for the Dorothy Beard Research Fund, his name was withdrawn. As Dr. Beard related to me, "McIntyre, find your proper place by merit, not by presumption. Integrity alone is not sufficient, push and insistence is degrading. Things arrived at by this means are sprinkled with dust that discredit and destroy reputations. The true way is the middle one, halfway between deserving a place and the other way, luck."

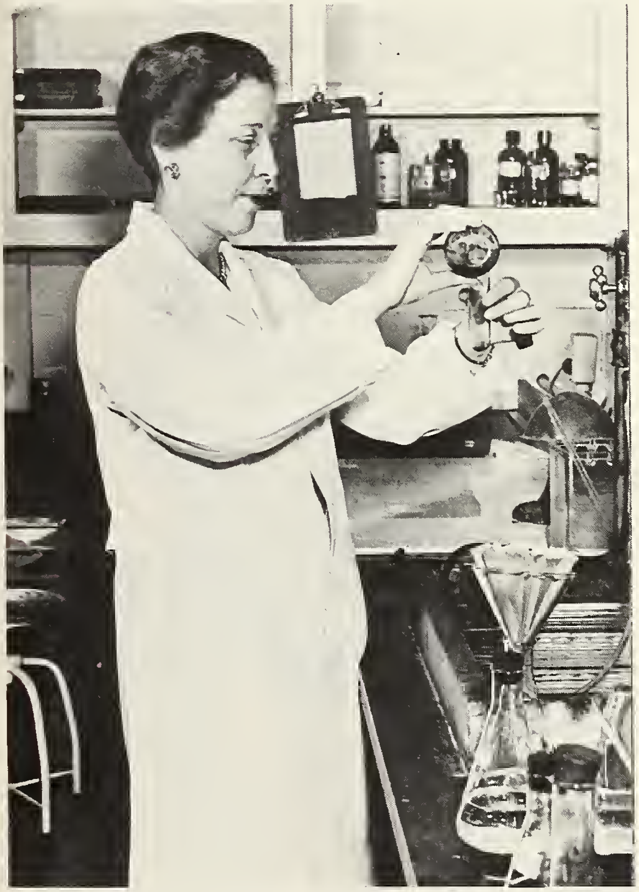


Figure 4. *Dorothy Beard working in the Bell Building virus research laboratory in 1956.*

The creation of a red brick building devoted to viral research and a teaching laboratory for dog surgery was an architectural landmark for Duke University. It was the first non-Gothic architecture on the Duke University campus. The name Bell Building was given in honor of the financier. Needless to say it was to remain a monument at the University. The research part of the building was named The Dorothy and Joe Beard Research Laboratory several years prior to their deaths. One must question whether the modernistic hospital now standing there would have ever been built if the architectural deviation was not first initiated by Dr. Beard. A multitude of viral research papers have emerged from the brick building. But the single largest contribution was producing men in the field of viral research world-wide which reads like "Who's Who" in medical research.

Another contribution goes unnoticed. How many lives were saved during World War II by his institution of a course in "Dog Surgery"? He was a dynamic teacher and insisted on sterile technique, a square knot, and the survival of the dog after ten different operations. These procedures left a lasting impression on uncounted students. Many medical students entered World War II with his being the only surgical instruction they received. The number of surgeons today influenced by his techniques is legion. His greatest asset was the ability to sense men's moods and adapt himself to each, genial or serious as the case may be. Dr. Beard was considered by all students to be unrelenting in perfection and uncompromising in discipline. Much to the amazement of outsiders, he was presented "Most Distinguished Teacher Award" by the Duke Alumni Association several years ago.

In this medical history of Dr. Joseph Willis Beard I must deviate to include my relationship. This I feel provides more insight than can be provided by anyone else.

A graduate of Louisiana State University in 1945, I was invited to Duke University Medical School for a medical school interview. After a standup bus ride from Baton Rouge, Louisiana to Durham, North Carolina I arrived after thirty-six hours of travel in nothing short of a disastrous condition. Joe and Dorothy Beard were there to meet me. He appeared seven feet tall, with bushy eyebrows, and mean looking on my first meeting with him (figure 5).

My efforts to gain admission were in vain. My inclination was to give up. After two days in Durham, a series of letters was exchanged between Joe and me. Failure was not a word in Dr. Beard's vocabulary. In answer to a letter I had

Figure 5. *Dr. Beard in 1945 when I first met him.*

written, Joe wrote, "You yourself said that if you didn't do well during your present semester you felt you ought not to go on. This would be a mistake, for it will be much simpler to take a new lease on life in new surroundings. Let's not give up the proposition. You said you wanted to study medicine, so let's go ahead and do it now and have no talk of quitting until you have definitely failed out." This is just an example of the encouragement Joe Beard gave. That was in June 1945.

In October 1945, I returned to Duke University as a graduate student and enrolled in Biochemistry, Statistics, and Scientific German. Scientific German was nothing short of challenging. With only two quarters of German at Louisiana State University, I was most inadequate in classroom activity. At this time Dr. Beard was in bed at his farm home recuperating from tuberculosis. He talked with the German Professor and obtained permission for me to drop from classroom activity and take the final examination for my grade. He explained to the teacher that he would teach me Scientific German.

For four months each Friday at five o'clock, Dorothy Beard drove me to the Beard farm. Dr. Beard taught me Scientific German from 6:00 p.m. to 11:00 p.m. on Fridays; from 8:00 a.m. to 11:00 p.m. on Saturdays, and from 8:00 a.m. to 5:00 p.m. on Sundays. Much to Dr. Beard's delight I took the Scientific German examination and received a B in the course, with As in Statistics and Biochemistry.

This four months of association with Dr. Beard was most enlightening. His conversations were punctuated with "hell" and "damn." He used the words for emphasis as no other person I have known. Their use was unnoticed in his speech and one came to expect them for reinforcement. This habit arose unquestionably in his childhood, working with road gangs and growing up in the Queensboro section of Shreveport, Louisiana. This area was the other side of the tracks, and demanded a tough personality. Having grown up in the same environment, I know toughness in talk and actions was a necessity. Fighting was commonplace and intellectual behavior was unacceptable among one's peers.

I felt if I continued at Duke the next semester I would have been admitted to Medical School. However, there was a war going on, and I could not wait to get an inguinal hernia repaired and enlist in the army. The impression Joe Beard left on a young nineteen-year-old graduate of L.S.U. was immeasurable.

Following my leaving Duke, correspondence was continued between Joe and me. The interesting phenomenon was that each letter was answered and a copy of the letter I had written was sent back with corrections of English and grammar.

In 1947, I was discharged from the Army and entered L.S.U. for a graduate degree in Physiology. On application I was admitted to Duke University Medical School. Dr. Beard and I made a pact that our first-cousin relationship would remain unknown.

In 1949, I entered Duke University Medical School. Dr. Beard and I became very close, a relationship I failed to see with his other acquaintances. Dr. Beard avoided close relationships with anyone (figure 6). An unloving mother,

Figure 6. *Dr. Beard in 1950.*

the tragic death of his brother, for which he was blamed, caused Dr. Beard to keep his distance from acquaintances for fear of being hurt. This behavior was not unknown to Joe. He said, ''Familiarity is never desirable with superiors because it is dangerous; with inferiors, because it is unbecoming; least of all with the common herd, who become insolent from sheer folly; they mistake favor shown them for the repeated need felt for them. Familiarity trenches on vulgarity.''

As a student of ''Dog Surgery'' with Dorothy and Joe Beard I became their target. A sterile technique along with a fifteen minute scrub with soap and water was repeated three times (45 min) for my first class. A square knot, two hand tie, was also a requirement. Their practice of riding my back gained me the sympathy of my classmates. My classmates surely felt I would not make the grade. Our confrontations were punctuated by Dr. Beard's comment, ''You are going to be the damnedest surgeon I've ever trained whether you like it or not.'' Those words ended our arguments over their demeanor toward me in the ''Dog Surgery'' class.

Occasionally I would go to spend the weekend at Dr. Beard's farm. I could mimic his vocabulary with the ''hell and damn'' to perfection. The weekends spent with Joe during medical school helped me to understand his demeanor and personality. I spent much time listening to his philosophy of life. He was the best read man and he could talk on any subject. He read not only paper pulp westerns, but also poetry, and every novel and scientific periodical he could get his hands on. He was truly the wisest man I ever knew. He spoke and wrote in five languages, four of which were self-taught. He was intolerant of intellectuals who were only fools. He respected the superior intellectuals of truth. He believed in God, but had little tolerance for most preachers since their knowledge was sparce and they were unable to communicate intelligently with him on Biblical matters. He said, ''McIntyre, man has one purpose on earth — either to reproduce himself or to grow something that would be lasting when his Maker calls. My papers are my children and a lasting contribution to mankind. When man can no longer make a contribution he has no reason to be here.'' This remark provided me with great insight into the last days of his life.

''Never have a companion who casts you in the shade.'' This best described Dr. Beard's philosophy; this is not to imply he was not friendly to any acquaintance. He worked with farmers around him and looked like a day laborer on the weekends. He cut hay, fertilized fields and milked dairy cows on the farm. His fields were immaculate; as the cows were milked he collected urine and feces in a trough that ran into a vat. In the spring he would fertilize his fields with this through a spray attached to a tractor. He truly was a leader in the Biblical sense for he was a servant to all.

While I was a student at Duke he set up the first electron microscope; I was present in the laboratory when the analysis of the chemical make-up of the virus was found to be a single strand of DNA.

In 1963, Dr. Beard broke his tibia and fibula in both legs in an automobile accident. Most men would have given up because healing was slow, but not Joe Beard — tenacious beyond imagination. After one and a half years of healing which left him two inches shorter, he was able to work, but not without pain.

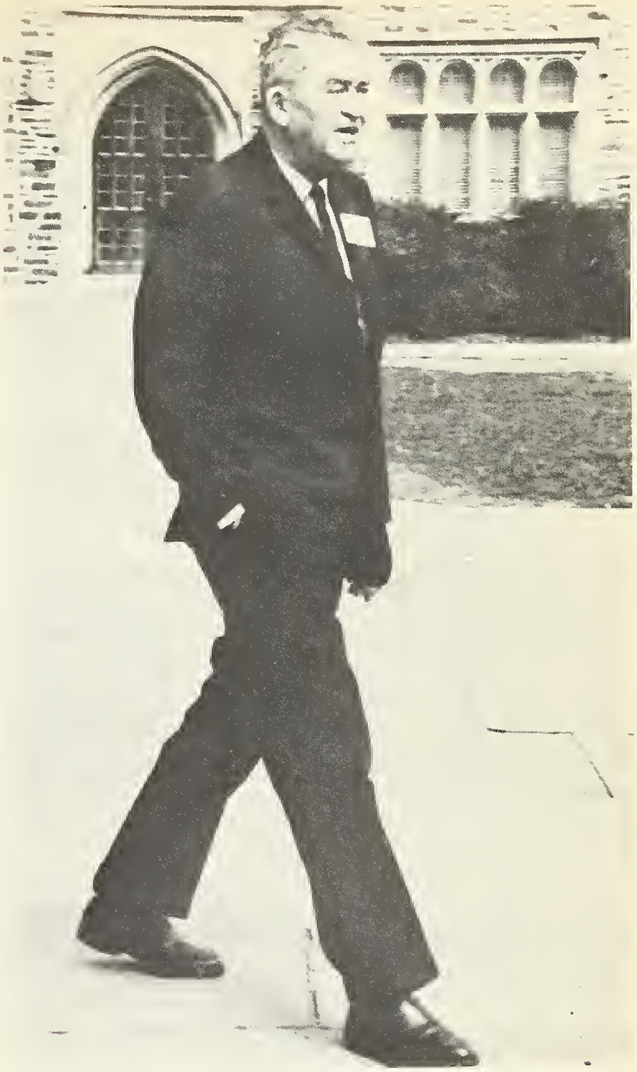


Figure 7. *Dr. Beard in 1970 on the Duke University Medical School campus.*

Joe received many awards but never mentioned any after his first disappointment. He received the Clowes Cancer Memorial Award for his work on leukemia in chickens. He established the relationship of a virus causing and resulting in the transfer of leukemia in chickens. Shortly afterward he was asked to be the Southern lecturer for the Sigma XI Society (figure 7). For one year he lectured at every university and college in the South. The first lecture was poorly received because he used perfect grammar. Recognizing that this was not his way of lecturing, he inserted his customary ''hell and damn'' and became an immediate success. He lectured to full houses thereafter and students from one school, after hearing him, would follow to the next speaking destination. Believe me, he could use those two words for emphasis and no one would ever think anything of it. His virus lectures and dog surgery classes were never dull with his ''artful'' usage of these words. Shortly before his retirement from Duke, at the age of 70, he received the Borden Award by the American Association of Medical Colleges. He was made a James B. Duke Professor on the faculty of Duke. In 1977, he received the Distinguished Teacher Award by the Duke Alumni Association.

After leaving Duke he became head of the Commercial Life Science Laboratory in St. Petersburg, Florida. He was a pioneer in molecular biology. He shipped virus all over the world that produced an enzyme, reverse transcriptase, which acted on bacteria. This virus in simple terms recombined DNA or caused gene splicing. His work in this field resulted in laboratories being established all over the world of a biogenetic nature. While at this laboratory these scientists created the first mumps vaccine, which is presently in use.

After leaving Duke, Dr. and Mrs. Beard and my wife and I exchanged visits several times. Once in 1974 he developed coronary insufficiency and was hospitalized in the ICU for twenty-four hours in Minden Medical Center, Minden, Louisiana.

In December 1982, Dr. Beard called me from St. Petersburg, Florida. He stated that he had been fired, and he wanted me to hear it from him first. He was 81 years old and I told him it was the best thing that ever happened to him. Upon investigation, I discovered he had not been fired, but when told to increase the price of the virus shipped by 100%, he quit. At my insistence he came to my home three weeks later. I noticed on the first night at dinner, every time he swallowed he coughed. I questioned him and learned this recurring problem had been getting progressively worse. He had lost fifteen pounds. The following morning a barium swallow revealed a Zenker's diverticular. At my suggestion that he return to Duke or some other prestigious place, he retorted "Why should I go anyplace else, when I know and have seen your work?"

The repair of the diverticulum was smooth and with hyperalimentation via tube feeding he soon gained twelve pounds and looked good. After two weeks of tube feeding he continued to cough when receiving food. Observation revealed a refusal to move the trachea upon swallowing. Three weeks after surgery he developed an incarcerated hernia. He refused to reveal this to me so the following morning Dorothy told me. Under local anesthesia I reduced and repaired the hernia. After two more weeks I threatened him with the nursing home if he didn't raise the trachea up and swallow properly. He started swallowing properly and I took him to my home, and with nurses around the clock for six weeks, he gradually but progressively improved.

Dr. Beard returned to St. Petersburg, but two weeks later was again hospitalized with a refusal to swallow properly. He had become a deliberate anorexia nervosa. Two months later he had lost twenty pounds more and his chest x-ray revealed oatcell carcinoma of the lungs. He died in less than three weeks.

Shortly after Dr. Beard's death, Dorothy Beard, who had both breasts removed for carcinoma about fifteen years before, developed carcinoma of the uterus. She died three months after the onset.

In October of 1984 my wife and I returned to the home of Dorothy and Joe Beard. The house was bare, and weeds had grown up everywhere. Over the garage was an office that was open. There was a bookshelf with two empty shelves, but on the bottom shelf was a book of poetry with the front cover missing. The book had been used at Centenary College by Dr. Beard. It had been a gift from George P. Evans, a professor visiting from Oxford, England. Inside the book were checked poems composed by Hewick, Lovelace, Suckling, Shakespeare, Milton and others. All poems checked dealt with love or sorrow. We then visited the old Episcopal Church cemetery in Hillsboro, N.C. where Dorothy and Joe were buried. Two small metal sticks with 3 x 5 inch cards marked their graves. Thus ended the era of a great man and his wife.

Dr. Beard was a scientist, surgeon, teacher, philosopher, dairy farmer, world traveler. What he accomplished in 81 years was more than could have been expected of ten men. He lived a controlled life, well planned, with no vision impossible.

Dr. Joe Beard was a genius who lived with tragedy. The expression of outward emotion, compassion, love, or gentle words were avoided. Tenacity beyond reason, kindness without show, courage in all convictions, unshakeable in character and humble to man, all describe Joe Beard as I knew him. "Adversity is strength" he told me one cold, snowy day. One must wonder what Joe Beard would have been with a loving mother, without the tragic loss of his brother, and with a successful first marriage with children.

Within myself I find these lines quite appropriate, "I loved you, not for what you were, but for what I was when I was with you. I loved you not only for what you made of yourself, but more for what you made of me."

A poet I am not, but I feel the following lines sum up Joe Beard in my lifetime:

I met a Man a day or two ago
Oh, I had heard of him, mostly
Bad and So and So
But when I met him
What I heard began to fade
Because you see, of me
A personal friend he had made.

We walked a bit and talked
a bit, and finally just us two
settled down to think as
the spring sky turned blue.
And in his conversation then
to me, his heart laid bare;
And friendship was the thing
for which we had a flare.

I think we are going to be OK
that man and me
Because the hardest part is
over and we trusted each
other, you see
And this I believe with
all my heart and soul
Our God stands and smiles,
as this story unfolds.

Dr. Joseph Willis Beard was a *mighty fine example* of what the Master had in mind when He said, "I will create a man."

Joseph Beard is one of the people who made the present Duke University Medical Center possible. He was the first member of the clinical departments to establish laboratories outside of the Departments of Anatomy, Physiology, Pharmacology, Bacteriology and Pathology. He was the first clinically trained scholar at Duke to be supported by research monies rather than by practice-generated funds.

When Duke Medical School opened, the decision was made that the clinical departments would have no laboratories. The clinician would collaborate with a member of the preclinical faculty. I was the first person to break this mold and establish a laboratory in a clinical department. When I came to Duke in 1947, I established research laboratories in the space assigned to Medicine. Walter Kempner had laboratory space, but it was in the space assigned to Physiology. All departments at Duke were being strangled because the preclinical faculty refused to expand outside of space physically attached to the medical school-hospital complex. They drew up plans for expansion each year, but they could not find the money to expand in Duke stone. Joseph Beard broke the bottleneck. He moved across the railroad tracks into a simple, two-story, expandable brick building. Dean Davison was so unsympathetic that for years the approach to Joe's building (named the Bell Building) was by a dirt trail that turned to mud with each rain. I joined up and helped finance the second floor of Joe's building. From then on, research endeavors in Medicine and Surgery were free to grow. Every few years we bought bricks and added space. Finally, Philip Handler, the Chairman of Biochemistry, joined up and moved his department into Bell Building. Duke was on its way as a major research center.

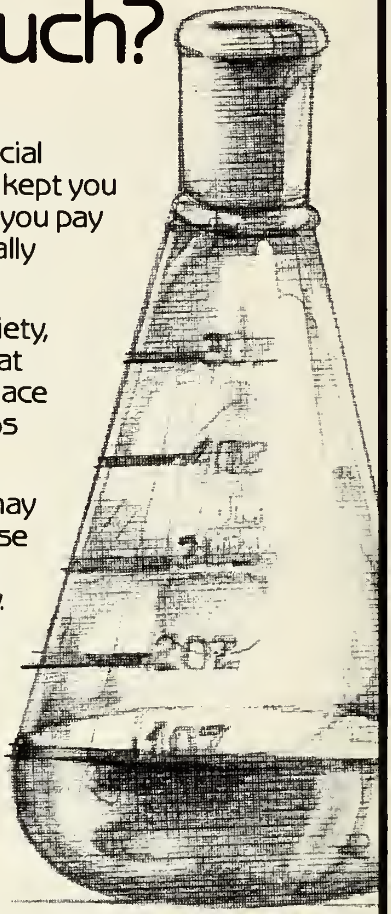
Beard ran his building with an iron hand. Every room had to have steam. There was no other way to insure sterility. No equipment was allowed in the corridors. If you didn't use your space, it was quickly assigned to others.

I bought a concrete mixer from Sears. I had no trouble in mixing cement, but I allowed mortar to crud the mixer. I went to see Joe at his farm. He showed me how to chip out the mortar and instructed me how to keep the mixer clean. During this time, he was raising chickens for his chicken leukemia studies. He supplied us with free chickens. I always hoped they were from the controls.

The Dorothy and Joseph Beard Research Fund, created by patents on equine encephalitis vaccine, supported the laboratory until the National Cancer Institute took over. The residual estate of Joe and Dorothy Beard will eventually contribute over a million dollars to support research at Duke.

One of the great men of Duke — Joseph Beard.

Eugene A. Stead, Jr., M.D.



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Book Review

Diane C. Cashman

Wilmington Yesteryear *by Robert Martin Fales, M.D., 152 pages plus index, 255 black and white photographs, published by the Lower Cape Fear Historical Society, P.O. Box 813, Wilmington, NC 28402. $28 (including N.C. sales tax, handling, and postage).*

On February 15, 1985, Wilmington's oldest practicing physician, Robert Martin Fales, M.D., retired from practice. His half century of medical service spanned an era marked by momentous change. Fortunately, Dr. Fales's memories of those changes have been captured in his informal memoir and pictorial history, *Wilmington Yesteryear,* which was published under the aegis of the Lower Cape Fear Historical Society in December 1984. As ''Heartbeat,'' the in-house publication of the New Hanover Memorial Hospital, noted, Dr. Fales's book provided ''an immortality'' to the physicians of yesteryear.

Dr. Fales can still remember his return to his hometown of Wilmington in 1935 and his entry into the private sector of the medical profession: ''My first order of business upon return was to find office space. Some of the well-established physicians maintained offices in the Murchison National Bank Building, but I was in no position to aspire to such lofty heights. Many doctors still practiced from offices located in their homes, and so I felt grateful to my mother, who had been widowed ten years, when she offered a downstairs room of her house as an office . . . (which) was ideal, since it had a separate entrance. I hoped it would not be too long before patients made their way to its door. I unpacked my books and diplomas, made courtesy calls on the local physicians, and made it known that I would be available for both day and evening office hours and would be happy to make house calls after dark. . . . At the end of my first month I had collected twenty-two dollars in cash and felt that those earnings represented a good start. In those days a doctor was supposed to start at the bottom and work up, and I certainly started at the bottom.''

If Dr. Fales ''started off at the bottom,'' he ended ''up at the top'' for in his half century of service he became one of Wilmington's most popular and respected physicians. In recent months he has also become one of the area's best selling authors. This new development resulted from the publication of *Wilmington Yesteryear*. Dr. Fales's keen memory, candor, and humor make his book delightful to read, although from his point of view the book's value is in its 255 photographs, which were selected from his historical slide collection that tops 1,100.

The book takes the reader back to the Wilmington of Dr. Fales's childhood, when the port city was cooled by ice and powered by steam. The characters that impressed him: hearty Masonboro Sound fishermen, dashing firemen, proud Confederate veterans, strict maiden lady school teachers, and German shopkeepers all come to life in picture and word.

Dr. Fales devotes one chapter to his medical education at Wake Forest and Jefferson Medical College, to his practice in Wilmington, and pays tribute to the physicians and nurses of the ''old school.'' A faded photograph shows surgeons operating without masks or gloves and the author recalls a surgeon stating that there was no need to scrub ''because a gentleman's hands are always clean!'' The medical chapter also includes photographs of Wilmington hospitals that have gone out of business: James Walker Memorial Hospital, Babies Hospital, and Community Hospital and includes a section on the James Walker Memorial Hospital School of Nursing.

Wilmington Yesteryear has received warm reviews and media coverage, and enjoyed brisk sales. The book's success is no surprise to those who know Dr. Fales. For more than a half century he has touched his patients' lives in a meaningful way and earned the respect of his professional colleagues. When Dr. Fales was autographing books at a local store, a customer was heard to say, ''I bought this book so I can hold in my hands what Dr. Fales has meant to me.''

From 2502 Market Street, Wilmington 28403.

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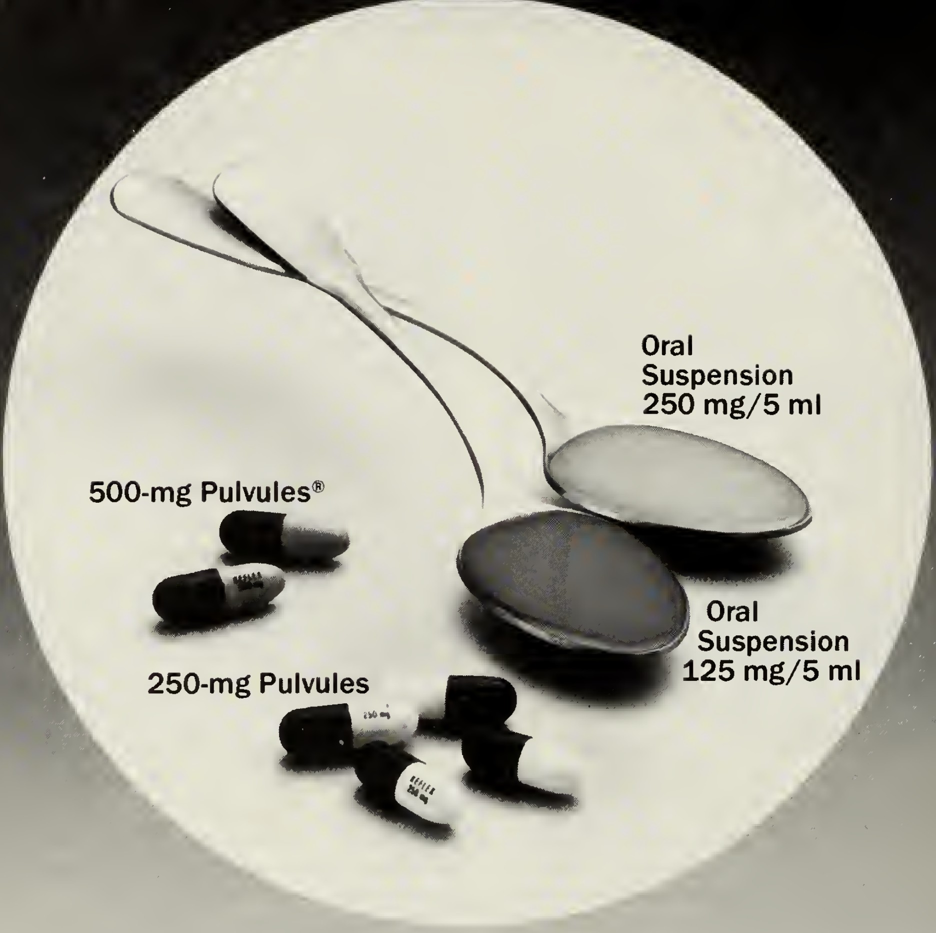

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IN STATE

May 17-18
Neurosurgery Laser Workshop
Place: Chapel Hill
Fee: $700
Credit: 15 hours Category I AMA; AANS-CNS
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

May 22
Antibiotics — The New Ones
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

May 23
Sexually Transmitted Diseases
Place: Chapel Hill
Fee: $20
Credit: 5 hours Category I AMA
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

May 24-25
Diagnosis and Treatment of Pediatric Hypersensitivity Diseases of the Lung and Gut
Place: Durham
Fee: $80
Info: Alexander Spock, M.D., Box 2994 DUMC, Durham 27710.

June 4
Crisis — Then & Now
Place: Charlotte
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

June 10-12
Surgery for Coronary Artery Disease
Place: Durham
Info: Robert H. Jones, M.D., Box 2986 DUMC, Durham 27710.

June 13
32nd Annual Mountaintop Medical Assembly
Place: Waynesville
Info: Debbie Ford 704/452-4772

June 13-15
Advanced Clinical Ultrasound
Place: Winston-Salem
Fee: $400
Credit: 16 hours Category I AMA
Info: James F. Martin, M.D., Box 229, Bowman Gray, Winston-Salem 27103. 919/748-4505

June 19
Cutaneous Manifestations of Systemic Illness
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

June 20
Crisis — Then & Now
Place: Elizabeth City
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

June 23-28
NC Health Promotion Wellness Institute
Place: Raleigh
Credit: 27 hours Category I AMA, AAFP
Fee: $260-370
Info: Jacqueline Rollins, Wake AHEC, 3000 New Bern Avenue, Raleigh 27610. 919/755-8018

July 5-7
15th Annual Sports Medicine Symposium
Place: Wrightsville Beach
Info: Alan Skipper, NCMS, Box 27167, Raleigh 27611. 919/833-3836

July 11
Crisis — Then & Now
Place: Hickory
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

July 15-19
Sonography of the Abdomen
Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: Dianne L. Willard, Bowman Gray, Winston-Salem 27103. 919/748-4505

July 16
Crisis — Then & Now
Place: Wilson
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

OUT OF STATE

May 25-27
Gynecologic Urology and Pelvic Surgery
Place: Hot Springs, VA
Fee: $250
Info: Eileen Hardigan, Box 538 MCV Station, Richmond, VA 23298. 804/786-0693

June 6-8
Rehabilitation of the Brain-Injured Adult and Child
Place: Williamsburg, VA
Fee: $275
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

June 12-15
Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Fee: $350
Credit: 15.5 hours Category I AMA, AAFP, NCMS
Info: Division of Dermatology, Box 3135 DUMC, Durham 27710. 919/684-2504

June 27-29
Bones, Joints, and Sports Injuries
Place: Virginia Beach, VA
Fee: $275
Info: Beth Winn, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

July 1-6
Mid-Summer Family Practice Digest
Place: Myrtle Beach, SC
Fee: $300
Credit: 30 hours AAFP
Info: NCAFP, Box 20146, Raleigh 27619.

July 19-21
5th Annual MCV Cardiology Conference
Place: Hot Springs, VA
Fee: $275
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

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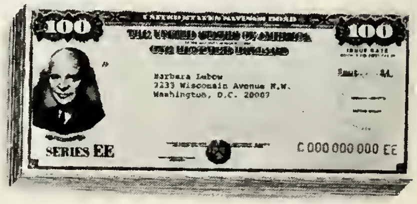

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(1.) On an official entry form handprint your name, address and zip code. You may also enter by handprinting your name, address and zip code and the words "Velosef–Computers in Health Care" on a 3" x 5" piece of paper. Entry forms may not be mechanically reproduced. **(2.)** Enter as often as you wish, but each entry must be mailed separately to: "COMPUTERS IN HEALTH CARE DRAWING," P.O. Box 3036, Syosset, NY 11775. All entries must be received by September 9, 1985. **(3.) Winners will be selected in random drawings from among all entries received by the National Judging Institute, Inc., an independent judging organization whose decisions are final on all matters relating to this sweepstakes. All prizes will be awarded and winners notified by mail. Only one prize to an individual or household. Prizes are nontransferable and no substitutions or cash equivalents are allowed. Taxes, if any, are the responsibility of the individual winners. No responsibility is assumed for lost, misdirected or late mail. Winners may be asked to execute an affidavit of eligibility and release. (4.)** Sweepstakes open only to physicians residing in the U.S.A., except employees and their families of E.R. SQUIBB & SONS, INC., its affiliates, subsidiaries, advertising agencies, and Don Jagoda Associates, Inc. This offer is void wherever prohibited, and subject to all federal, state and local laws. **(5.) For a list of major prize winners, send a stamped, self-addressed envelope to: "COMPUTERS IN HEALTH CARE" WINNERS LIST, P.O. Box 3154, Syosset, NY 11775.**

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INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli*, *P. mirabilis*, *Klebsiella* species, and enterococci (*S. faecalis*).

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

Other antibacterial agents — Bacteriostats may interfere with the bactericidal action of cephalosporins in acute infection; other agents, e.g., aminoglycosides, colistin, polymyxins, vancomycin, may increase the possibility of nephrotoxicity.

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Diuretics (potent "loop diuretics," e.g., furosemide and ethacrynic acid) — Enhanced possibility for renal toxicity.

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Drug/Laboratory Test Interactions: After treatment with cephradine, a false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®. False-positive Coombs test results may occur in newborns whose mothers received a cephalosporin prior to delivery. Cephalosporins have been reported to cause false-positive reactions in tests for urinary proteins which use sulfosalicylic acid, false elevations of urinary 17-ketosteroid values, and prolonged prothrombin times.

Carcinogenesis, Mutagenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential or mutagenesis.

Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 4 times the maximum indicated human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cephradine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers: Since cephradine is excreted in breast milk during lactation, exercise caution when administering cephradine to a nursing woman.

Pediatric Use: Adequate information is unavailable on the efficacy of b.i.d. regimens in children under nine months of age.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported following use of cephradine: G.I. — Symptoms of pseudomembranous colitis can appear during antibiotic therapy; nausea and vomiting have been reported rarely. Skin and Hypersensitivity Reactions — mild urticaria or skin rash, pruritus, joint pains. Hematologic — mild transient eosinophilia, leukopenia and neutropenia. Liver — transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage. Renal — transitory rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others — dizziness, tightness in the chest, and candidal vaginitis.

DOSAGE: Adults — For respiratory tract infections (other than lobar pneumonia) and skin and skin structure infections: 250 mg q. 6 h or 500 mg q. 12 h. For lobar pneumonia: 500 mg q. 6 h or 1 g q. 12 h. For uncomplicated urinary tract infections: 500 mg q. 12 h; for more serious UTI, including prostatitis, 500 mg q. 6 h or 1 g q. 12 h. Severe or chronic infections may require larger doses (up to 1 g q. 6 h). For dosage recommendations in patients with impaired renal function, consult package insert.

Children over 9 months of age — 25 to 50 mg/kg/day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae*: 75 to 100 mg/kg/day in equally divided doses q. 6 or 12 h but not to exceed 4 g/day. Dosage for children should not exceed dosage recommended for adults. There are no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

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Letters to the Editor

Blood and the Jehovah's Witness

To the Editor:

I continue to enjoy the *North Carolina Medical Journal*. I have just read the February issue from cover to cover. I was most intrigued with the Physician's Forum concerning patients who refuse life-saving treatment.

I had a recent interesting experience with a Jehovah's Witness. She originally refused to have blood before surgery to remove a large cystic thecoma. We were willing to operate without transfusions out of our respect for her religious belief. Prior to surgery she changed her mind and received two units of red blood cells. The operation was successful but unfortunately she developed postoperative bleeding from post-transfusion thrombocytopenic purpura. She is probably the first and only Jehovah's Witness to develop this condition because they are rarely transfused. She was treated by plasmaphoresis on two occasions and recovered uneventfully.

Post-transfusion thrombocytopenic purpura is an exceedingly rare complication, only 30 cases having been reported in the literature through 1980.

This patient was nearly smarter than her doctors!

Robert K. Yowell, M.D.
2609 North Duke Street
Durham 27704

Physicians in the 1985 Legislature

To the Editor:

Having known Harold R. Silberman, M.D., for over twenty years, I was not surprised to see the excellent editorial he submitted regarding physician involvement and interaction with the members of the 1985 North Carolina Legislature. Harold wisely and appropriately reminds us that physicians should and must ''become involved'' with pending legislation that affects not only the practice of medicine, but more importantly, the preventive medicine issues.

After observing tragic emergency room cases resulting from nonuse of seat belts by adults, or lack of child passenger restraints, or even those sometimes severe injuries resulting from motor-cross racing, who is better able than physicians to alert our community to the ''medical'' pros and cons of the bills under consideration.

It goes beyond just volunteering to be a ''key-contact'' physician. I have volunteered and served as a key-contact physician for several years. I have found this to be a stimulating, rewarding, and very productive experience. I have written to each of my legislators indicating my interest in being available to them to discuss or offer insight on any issue that I might be able to explain from organized medicine's perspective as well as from the perspective of an individual tax-payer. I basically believe that most of the issues that physicians can be helpful in are not partisan at all, and I personally have had no difficulty whatsoever as a registered Republican getting heard by and interacting with responsible Democratic legislators. I was not clever enough to provide my paging beeper number to my state representative and/or senator, but I think Harold provides a useful suggestion in his editorial, which I will follow up on.

The point is, we need to stay in touch with our legislators and be ''available'' in an ongoing sense other than simply waiting until some threatening issue comes up to begin a frantic ''lobbying'' effort. I commend Harold for his editorial and for his efforts to take the time to get involved.

F. Maxton Mauney, Jr., M.D.
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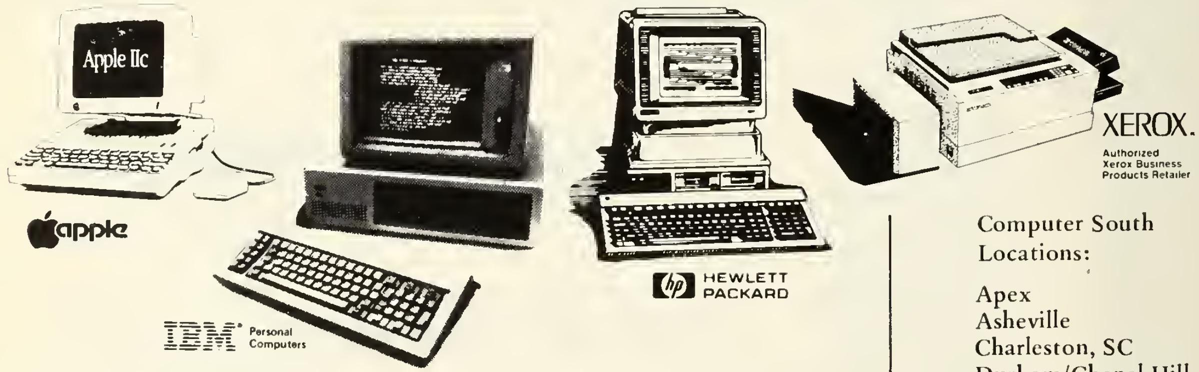

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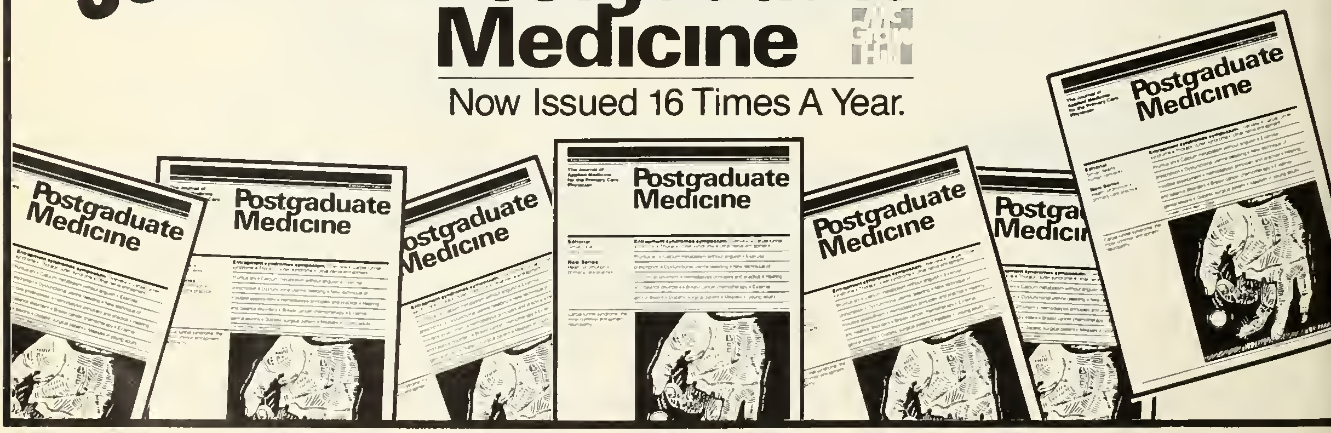

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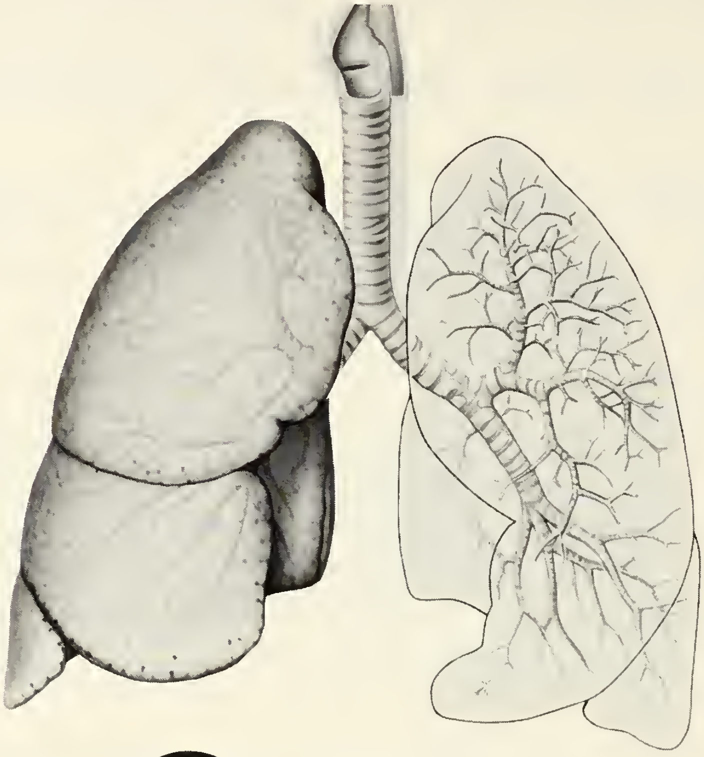
Consider the causative organisms...



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Contraindication Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile.* Other causes of colitis should be ruled out.

Precautions: *General Precautions* – If an allergic reaction to Ceclor® (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy – Pregnancy Category B – Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor® (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers – Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children – Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain – Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic – Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic – Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal – Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note Ceclor® (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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SPECIAL ARTICLE

Family Medicine at Duke: Excellence Defined

Robert J. Sullivan, M.D.

THIS month at Duke, the Life Flight helicopter was inaugurated, the state's first human heart transplant was successfully completed, and the Family Medicine program was scheduled for termination. Duke is clearly on the move, and the direction seems increasingly clear. Each of these events has been accompanied by some controversy, particularly the Family Medicine decision since it simultaneously affects so many people throughout the region and perhaps elsewhere.

The Family Medicine residency program was inaugurated at Duke in 1972 owing to a fortuitous set of circumstances. Federal and state money was available, the department of Community Health Sciences headed by a respected faculty member wanted the program, and community physicians were pressing Duke to re-establish a commitment to primary care in the state. Until 1947, Duke was heavily oriented toward clinical practice under the leadership of Dean Davison. The expansion of federally funded research programs following World War II was greeted with enthusiasm by the faculty who successfully garnered major support from this resource. The school grew rapidly and the specialists, sub-specialists, research-oriented physicians and Ph.D.'s soon outnumbered those generalists who treated patients not requiring the services of specialists. Although uneasy about this transition, Dean Davison could not prevent it. Following his retirement, his medical center successors further expanded the growing image of Duke as an innovator in medical research and as a referral source for the southeastern region.

Of course, Duke was not alone in this technologic thrust. Most major medical centers were following much the same course. By the mid-1960s the family medicine movement arose nationally to re-define the role of physician generalist. The generalist concept was not universally hailed with enthusiasm by medical center specialists. Particularly those in pediatrics, internal medicine and obstetrics/gynecology were skeptical that one person could know enough to do the job well. Perhaps more disturbing was the perceived criticism of the way specialists were conducting business. In effect, the family practitioner seemed to be laying claim to the mantle of "physician" while others were relegated to the role of "doctor."

To the degree individual teaching institutions felt motivated to respond to the call, family medicine programs sprang up throughout the nation. However, for a multitude of reasons, few privately-endowed medical centers in Duke's circle of equals took the plunge. When Duke, after rejecting two proposals, finally proceeded in 1972 to create the Family Medicine program, it was not done with unanimous faculty acclaim.

Logic dictated the new program be placed in the local community hospital where an enthusiastic group of practicing primary care clinicians and specialists welcomed the strengthening of their own residency program. Duke University Hospital, already overcrowded with referral patients, staffed by subspecialists and replete with a full complement of house staff, remained off-limits to the new program faculty and house officers. This arrangement meant the new Family Medicine program was out of sight, but not out of mind.

Under capable leadership, the Family Medicine program at Duke rose to national prominence. It served the region by producing a substantial number of primary care physicians who located throughout the state. The program emphasis on community care provided a point of identity and contact with Duke University for many who long felt estranged from the technologically oriented medical center. Duke became eligible for Area Health Education funds as a result of its production of primary-care physicians and through participation in the statewide network of education. The family medicine movement got a tremendous boost from the presence of training programs at all four medical schools in the state, the largest of which was located at Duke. The medical center reputation as a good citizen was enhanced throughout the state. Unfortunately, internal problems persisted.

The resident and faculty physicians at the Family Medicine center were located on the campus of Durham County Hospital three miles from Duke Medical Center. Their daily working relationships with community specialists led them to refer many patients to the physicians at Durham County Hospital. Absence from Duke Medical Center inhibited their knowing which Duke specialist to call upon when addressing a particular patient's problem. Primary care physicians are acutely aware of their responsibility for coordinating care and feel uneasy referring patients when they don't personally know the specialist. In addition, patients sent to the Medical Center complained about problems with parking, delays in the clinic and high costs when compared with community options. In prior years, the absence of alternatives would have made the trip to Duke inevitable. However, the growth of medical expertise in the Durham community, largely a result of Duke's own spe-

---

From the Department of Medicine, Duke University Medical Center, Durham 27710.

cialty training programs, increasingly offered excellent alternatives which many patients specifically requested. Duke perceived its successful thrust in the area of family practice to be diverting patients to community physicians rather than expanding the Duke referral base.

A surprising paradox developed simultaneously as community physicians came to perceive the Duke Family Medicine program as an intrusion into community practice that diverted patients from their offices. When pre-paid practice plans arrived, they were initially viewed by community physicians with disdain until the Family Medicine program jumped at the opportunity and promptly expanded its service population. A ground-swell of uneasiness was building within the community. Local physicians loved the resident services at their hospital, but had not realized when they sought affiliation with the Duke Department of Community and Family Medicine that this new brand of resident and support faculty would establish their own office complex and compete for available patients. Many saw use of the Duke name (Duke Family Medicine Center) as an unfair advantage and pressured the University to limit the function of this new creation.

Additional criticism of the Family Medicine program came from the Duke Medical Center Internal Medicine, Pediatrics and Obstetrics/Gynecology house officers and their attending physicians from Duke who accepted responsibility in rotation for supervising the training program on the wards at the Durham County Hospital. They had trouble understanding the orientation of the Family Medicine house officers who had been carefully selected for their intellect, orientation to patients and their families, and commitment to community needs. The medical center personnel interpreted lack of interest in bench research and pursuit of balanced working hours as evidence of inferior commitment and ability. In reality it was a clash of cultures.

Thus, the Duke Medical Center administration was beset with complaints about the Family Medicine program from three sides. This internal tension was largely unappreciated outside the walls of the Medical Center or the Durham community.

Faced with escalating costs and dwindling resources, the leadership of Duke Medical Center initiated a self-assessment in 1984 to determine areas of unusual strength or expertise on which to place emphasis in the next decade. Family Medicine was given a low priority in this review. When the current Family Medicine division chief (Samuel Warburton) announced his resignation in early 1985, it became imperative to decide the fate of the program. If it were to continue, an intensive recruitment campaign was needed for a successor. And with that campaign came the need for a Medical Center consensus and re-commitment to family medicine. That consensus had become increasingly unlikely.

Since objective internal assessment of the Family Medicine program was impossible, an outside consultant was sought to assess Duke's primary care options in the next decade. The report by Lewin and Associates of Washington, D.C. provided some additional insights and options.

The study called for an independent and dedicated effort in primary care. Noting the specialty orientation of the Departments of Medicine, Pediatrics and Obstetrics/Gynecology, the Lewin report suggested Family Medicine be given expanded responsibility in this area. The success of the program in reaching out to the community and its value as a point of contact for rural physicians and hospitals was emphasized. It was also seen as a valuable resource for future medical center participation in the pre-paid practice movement.

The report also carefully noted the long-standing friction between the Family Medicine program and the rest of the Medical Center. It traced the problem to differing sets of values, equally strongly held. Both groups were committed to excellence; but their definitions diverged. Family Medicine (holistic, integrative and humanistic) challenged deep rooted traditions in academic medicine and clinical practice. The report noted that the decision about the future of the department must resolve these fundamental problems.

The Medical Center faced a clear choice. The Family Medicine program could not continue without a leader. Recruiting a replacement meant either maintaining the program's isolation or full acceptance in the Medical Center. The latter concept was neither practical nor acceptable to the department chairmen at Duke. With the current state of tension likely to persist indefinitely, recruiting a capable leader for Family Medicine would be impossible. Accordingly, with reluctance, the decision was made to close all clinical programs of the Department of Community and Family Medicine and relocate them to newly-expanded primary care divisions within the Departments of Medicine, Pediatrics and Obstetrics/Gynecology. Primary care would henceforth develop at Duke within specialty lines. The conflict was resolved.

Or was it? The magnitude of the decision and far-reaching ramifications have only now begun to surface. More will surely emerge in the ensuing months and years. The Department chairman (Harvey Estes) resigned his chairmanship, and began a movement for keeping a Family Medicine Program — not allied with Duke — alive. Family Medicine forces throughout the state and nation took personal afront and openly criticized the decision. Duke's contractual arrangements with the Durham County General Hospital were thrown into doubt. Capitation funds from the state for training physicians were brought into jeopardy. The Student Health and Employee Health programs for the University were suddenly threatened with relocation and loss of existing staff. The Departments of Medicine, Pediatrics and Obstetrics/Gynecology suddenly were faced with responsibility for ongoing care of a large number of Family Medicine patients who might wish continual service from Duke. The uncertainty surrounding this transition was reflected in newspaper interviews published daily.

Beyond the details of the Family Medicine program closure lie some very large issues that will be of major importance to Duke in the years to come. Our system of medical care financing is undergoing a revolution. The impact is sure to be as great on all medical centers as was the arrival of federal research funding following World War II. The public is unhappy with existing health care arrangements and feels they are too costly, too technical, lacking in personal attention, and inconvenient. Pre-paid practice plans will compete for consumer participation by satisfying their demands. A doctor surplus will make it possible to hire the manpower to provide whatever services people want in a fashion they desire. Integrated organizations combining insurance, management, financing and professional services from primary care through secondary and tertiary levels will dominate the medical care picture. Medical centers will dwindle in stature as this movement gains momentum. Viewed in this light, Duke's decision to truncate its excellent primary care operation and community access link represented by the Family Medicine program seems to many persons to be most unwise.

Viewed in another light, Duke could be said to have had no choice. Future federal funding for family medicine manpowered training is in jeopardy. Family Medicine had developed no base of research funding. The Family Medicine program, if it is to survive, must garner pre-paid health plan support. But cost-competitive health care is impossible at a training site. When alternative practices open in the Durham area, the Family Medicine program risks being underbid. In addition, effective integration of non-competing delivery components is essential for any organization that expects to meet tomorrow's market. In 13 years of operation, the program had not created significant bonds with existing clinical departments. The off-campus site and Durham County Hospital connection made true long-range Family Medicine integration with Duke University Medical Center difficult if not impossible. Relocation to the Medical Center was educationally unsound and politically impractical.

The Duke University faculty have previously made difficult decisions. In the past five years, they closed the School of Education and the Undergraduate Nursing program. The Forestry School barely escaped a similar fate but pulled itself from the precipice by diligent effort. Any major corporation faces such tough decisions from time to time. If a valuable subsidiary, no matter how pertinent to long-range future growth, is proving destructive to the fabric of the organization, it must be set free. So it was with the Family Medicine program at Duke.

We come again to the events of the month. Judging from initial utilization, the helicopter service has met a great need. The pioneering efforts of the surgery service in transplant technology have received national attention. Interviews with beleaguered Family Medicine faculty are receding. As with the Schools of Nursing and Education, this too will pass. The Duke University Medical Center faces, as it always has, the awesome continuing task of competing successfully in today's changing climate for recognition as a regional and national resource. Such an effort requires continual growth, trial and reevaluation. It does so now with redefined clarity of purpose and unity of spirit . . . for better or worse. At least it can be said that Duke tried while few of its peers even made the attempt. The Family Medicine program Duke created was recognized as one of the best. It is indeed unfortunate for many, both within the University and throughout the state and region, that the trial proved unsuccessful.

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SCIENTIFIC ARTICLE

You're in for a Treat: Asparagus

Jeremy Sugarman and Francis A. Neelon, M.D.

• *Many people notice an unpleasant odor to their urine after eating asparagus.*

A 47-year-old white married man who had always enjoyed excellent health telephoned the physician's office worried that he might be seriously ill. After working in the garden the previous day, the patient noted a disgusting, "sulfurous" smell to his urine. He was concerned he might have been poisoned in someway, but otherwise felt well. On questioning, the patient recalled eating asparagus at supper the day before. He was reassured that many people notice a characteristic odor in their urine soon after the ingestion of asparagus and his "symptom" would probably be relieved if he avoided asparagus. The patient was instructed to call back if his urine remained fetid without the prior ingestion of asparagus. Of interest, the patient had eaten asparagus several times before and had not noticed the odor in his urine, although he remarked that the smell was "not unfamiliar." A follow-up telephone call to the patient one week later confirmed that the patient had not eaten any more asparagus and the smell of his urine had returned to normal.

Although it was easy to reassure this patient of his "normality," we began to wonder about what actually caused the characteristic odor of urine following the ingestion of asparagus. Is there a specific compound produced as asparagus is metabolized? If so, do all people produce the compound? How come the patient only now noticed a smell in his urine and had not on those previous occasions when he had eaten asparagus? We were fascinated by what we found as we investigated these questions and surprised by the number of people who found the topic interesting. Indeed, it is a subject which has fascinated people from all walks of life, from potentates to peons.

The Role of Asparagus in the History of Medicine

"Before asparagus was used as a food it had quite a reputation as a medicine for almost anything from the prevention of bee stings to heart trouble, dropsy, and toothache!"[1] In the Greek herbals, Dioscorides claimed that asparagus "doth mollifie the belly and prouoke vrine."[2] In the seventeenth century, John Gerarde discussed the virtues of asparagus in *The Herbal or General History of Plants:* "They somewhat provoke urin, are good for the kidneys and bladder, but they yeeld little nourishment to the body, and the same moist, yet not faulty: they are thought to increase seed and stir up lust."[3]

The first mention of the inimitable odor imparted to urine by eating asparagus seems to have been made at the turn of the eighteenth century in a treatise on foods written by Louis Lemery. "Sparagrass eaten to Excess sharpen the Humours and . . . cause a filthy and disagreeable Smell in the Urine, as every Body knows."[4] Before immortalizing Lemery as the esteemed discoverer of the odor, it should be realized Chaumeton gave Avicenna credit for this discovery.[5] Nonetheless, an examination of Avicenna's *Cantos* did not furnish any mention of asparagus whatsoever. In 1732, the noted writer and physician to Queen Anne of Britain, John Arbuthnot, wrote *Practical Rules of Diet in the Various Constitutions and Diseases of Human Bodies.* Under the heading of diuretics, Arbuthnot includes "vegetables which are aromatick and balsamick, Saffron, Asparagus, Nutmeg; those affecting the Urine with a Odour."[6]

Scientific Investigations of the Odor

Over the past century, two approaches have been taken to explain why some people are aware of the characteristic odor of urine after the ingestion of asparagus, while others are not. At first, work focused on identifying a factor in the urine which caused it to smell; those people who reported the odor in their urine became known as "excretors" and those without the odor were in turn called "nonexcretors." The first candidate compound was proposed in 1891 by M. Nencki who tentatively nominated a mercaptan (figure 1a), methanethiol (figure 1b), as the etiologic agent.[7] Mercaptans are compounds that substitute sulfur for oxygen in an alcohol group; mercaptans are the odoriferous agents in many pungent substances including skunk spray, garlic and fresh-cut onions. In 1932 Gautier described the rapid appearance of the odor in urine, finding it as soon as seventy-five minutes after ingestion of asparagus.[8] Twenty-five years later, another mercaptan, 2,2′-Dithiolisobutyric acid (figure 1c), was isolated from asparagus. Although the compound has a slight odor, researchers at that time felt it "apparently is not the precursor of the characteristic odor of the urine . . . since no odor resulted when two individuals took 10 mg each of dithiolisobutyric

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From the Division of General Internal Medicine, Duke University Medical Center, Durham 27710.

The authors thank Susan C. Smith for the artistic contribution and Marta Conkling for the culinary.

acid orally."[9] A few years later, a methylsulphonium salt of methionine (figure 1d) was isolated from asparagus. Unfortunately, the methylsulphonium salt is an unlikely cause of the odor since it is found in vegetables not causing an odor in the urine.[10] Despite efforts to isolate new compounds, attention returned to methanethiol when Allison and McWhirter[11] gave asparagus to 115 individuals and measured methanethiol in their urine. They found 46 individuals to be excretors, and 69 to be non-excretors, of methanethiol; they concluded "that the excretor character is controlled by a single, autosomal dominant excretor gene."[11] Interestingly, McKusick mentions that a non-excretor may become an excretor during pregnancy.[12]

Because methanethiol is rapidly oxidized, White suspected it could not be the odor-producing compound. He was able to isolate two unusual sulfur compounds in the urine of a subject who had eaten asparagus: S-methyl thioacrylate (figure 1e) and S-methyl 3-(methylthio) thiopropionate (figure 1f).[10] White reported that the addition of these compounds to urine imparted the characteristic odor to previously non-odorous urine. Two years later, other researchers found three, rather than two, novel sulfur-containing compounds in post-asparagus urine, but did not completely characterize them.[13] The difficulty in isolating a specific mercaptan might be explained by the high reactivity of these compounds and their rapid transformation as pH changes. It is obvious that human physiology, for instance in terms of gut bacterial flora or urine pH changes, varies between individuals, and also changes from time to time within the same individual. These variations may well account for the many compounds implicated as causing the odor. We conclude from our review of these studies that the final answer is not yet in! We cannot say with certainty whether (and which) one or many compounds are responsible for the odor of asparagus urine. Nor is it certain that some people do not make the odoriferous compound(s) while others do, but this seems plausible as an extension of Allison's studies on methanethiol.

Figure 1. *Compounds implicated as producing an odor in urine after eating asparagus.*

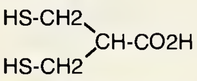
A. A Mercaptan

R-SH

B. Methanethiol

CH3-SH

C. 2,2′-Dithiolisobutyric acid

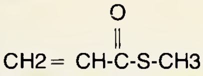


$(\text{HS-CH2})_2\text{CH-CO2H}$

D. Methylsulphonium salt of methionine

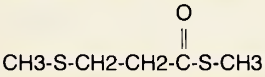
(CH-3) 2 S+ CH2-CH2-CH (NH2) COO-

E. S-methyl thioacrylate



$\text{CH2}=\text{CH-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-S-CH3}$

F. S-methyl 3-(methylthio) thiopropionate



$\text{CH3-S-CH2-CH2-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-S-CH3}$

A fresh approach to the study of the variability in the perception of the odor was taken in 1980, when Blondheim suggested "that the excretion of odorous substances in urine after eating asparagus might be universal, but that the ability to detect their odor varied."[14] Thereupon, the ability to perceive the odor was investigated. In a careful study Lison et al found, "the detection of the odour constitutes a specific smell hypersensitivity. Those who could smell the odour in their own urine could all smell it in the urine of anyone who had eaten asparagus, whether or not that person was able to smell it himself."[14] They found that 10% of 307 subjects tested were "able to smell it at high dilutions, suggesting a genetically determined specific hypersensitivity."[14] The experiments of Lison and his colleagues suggest that at least part of the reports that some individuals do not make malodorous urine after eating asparagus is due to an inability of those individuals to sense the odor at all. Some individuals can only distinguish the smell in a highly concentrated urine — this may explain why our patient "suddenly" became aware of the odor relatively late in life.

An Experiment

Our literature search left us with several questions unanswered regarding the variability in reporting an odor to the urine after eating asparagus. Does everyone make the odor, but only some people smell it? Does everyone smell the odor, but only some people make it? Do both conditions (excretion/non-excretion; perception/non-perception) prevail? To explore these questions, we conducted a small clinical study. Nineteen healthy volunteers (seven men, twelve women) were recruited from the faculty, staff and students at Duke University Medical Center. Urine samples were collected from each subject immediately before the start of the experimental session. Each subject judged whether his own urine specimen had an unusual odor. A small meal of fresh steamed asparagus with lemon and butter, French bread and carbonated water was then served. Postprandial urine specimens were obtained from all subjects. Again each subject was asked to record whether any unusual odor was present. The authors, both known-excretors and known-perceivers, were kept blind of each subject's self report and refrained from eating asparagus during the experimental session. In a double-blind randomized fashion, each author smelled the 38 separate urine specimens and noted whether the urine contained the characteristic odor. The authors resmelled and reached consensus on 10 specimens where there was initial disagreement.

Results. The results of the study are displayed in table 1. Fifteen of the 19 subjects were found to be excretors. One-third of the excretors could *not* perceive anything unusual in their post-prandial urines, while both investigators could. Importantly, 4 of 19 subjects were felt to be non-excretors. That is, the investigators could not detect an unusual odor in their urine.

The authors found it more difficult than expected to accurately detect the odor. Six subjects were found to be false positives; that is, the authors thought their initial urine specimen contained the odor. One of these six subjects had had asparagus for dinner the previous evening, something we had not controlled for. The other subjects were not

Table 1.
Patterns of Excretion and Perception of Odor in Asparagus Urine

Investigator Perception of Odor	Self-perception of Odor		
	YES	NO	N
Excretors	10	5	15
Non-excretors	1	3	4

questioned about this. Both authors had some difficulty discerning the difference between the acrid smell of a very concentrated non-asparagus urine and a weakly positive post-asparagus urine. One subject was a false negative, reporting he could smell something unusual in his postprandial urine when neither investigator felt his urine had the characteristic odor.

Discussion. Our results support both theories explaining variability in the odor of urine following the ingestion of asparagus. The investigators, being known perceivers, found that four subjects did not produce an unusual odor after ingestion of asparagus. One of these subjects was able to recognize an unusual odor in a known positive urine. If the theory suggesting that only a variation in sensitivity of smell accounts for the differential recognition of the odor, these data would not be expected since two known perceivers (the authors) could not smell an odor in those four urines. These results suggest that some people are excretors while others simply are not.

On the other hand, five of the fifteen subjects who were excretors could not perceive the odor in their own urine; two of these five subjects were tested against another strongly positive urine and could detect no odor. Thus, it appears that both theories are (partially) correct: some people are excretors while others are non-excretors; some people are perceivers while others are non-perceivers.

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"What cha' plantin', Neighbor?"
"Asparagus."
"Don't cha' know it takes two years to make itself known?"
"Nope! It takes about one hour after you eat it."

AN ODE OR VILLAINELLE FOR ASPARAGUS

Ah, stop time's arrow in its flight!
It takes two long years 'til it appears:
The asparagus stalks by night.

Set the table! For dinner tonight
It's sparrowgrass, a feast served here
That stops time's arrow in its flight.

Supplicants enamored by the sight:
Love's ruddy apple; the green spear
Of asparagus stalks by night.

The taste, the roué palate's delight
Which knows not yet the thing to fear.
Oh, stop time's arrow in its flight.

The Gargantuan fete makes bellies tight;
An urge to miction soon appears —
The asparagus stalks by night.

Behold! The urine's malodorous might,
Enough to make the dry eye tear
And stop time's arrow in its flight;
The asparagus stalks by night!

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SCIENTIFIC ARTICLE

Increase in Health Professionals in North Carolina: 1978-1983

Mary Anne Salmon, Priscilla A. Guild and Shannon P. Hallman

• *Health professionals are increasing in number faster than North Carolina's population, representing real improvement in the supply of health care.*

THOUGH vital statistics and data on health care facilities have long been regularly published in North Carolina, current information on the state's health workers has become available more recently.

Since 1974 the Health Services Research Center, University of North Carolina at Chapel Hill,[1] has maintained data on licensed health manpower in the state through a cooperative effort with each licensure board.

Currently, files are maintained for the following professions:

chiropractors
dental hygienists
dentists
doctors of medicine
doctors of osteopathy
licensed practical nurses
nurse practitioners
optometrists
pharmacists
physical therapists
physical therapy assistants
physician's assistants
podiatrists
psychologists
registered nurses

These files are updated yearly, current as of October 31, based on data from each of ten boards which either license or register these professionals who practice in the state.

Figures 1-3 draw from these files to show the changes in numbers of health professionals which occurred in the five year period ending in 1983. Although North Carolina remains behind the country as a whole in its ratio of doctors to population,[2] these figures, taken together with figure 4, which shows the state's increase in population, indicate that the numbers of physicians and other licensed health workers in North Carolina has increased faster than the general population during that period.

As shown in figure 1, the number of nonfederal, nonresident physicians practicing in the state grew 31 percent (from 6433 in 1978 to 8426 in 1983). However, relatively little of this growth was in the primary care specialties. The number in general practice declined almost 25 percent while the numbers in pediatrics and ob/gyn showed modest increases. The exception to the slow growth trend in primary care was family practice which showed the largest proportionate gain of the primary care specialties. This brought the number of family practitioners in 1983 almost up to the level of internists, the most prevalent of the primary care physicians. By contrast to most primary care categories, physicians in specialties not providing primary care, already the largest group, experienced a forty-six percent increase: from 3204 in 1978 to 4666 in 1983. In 1983, fifty-five percent of North Carolina's doctors were in specialties outside of primary care.

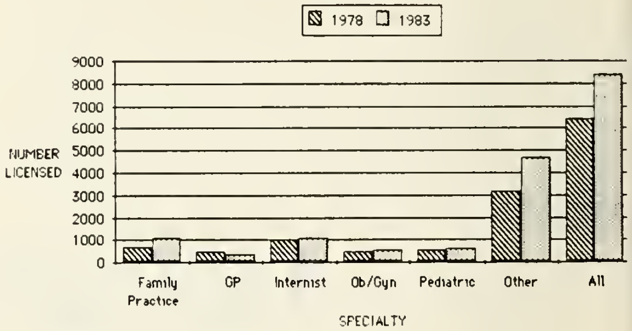

Figure 1. *North Carolina Physicians 1978 and 1983.*

The supply of nurses in North Carolina also grew during the period from 1978 to 1983. Figure 2 illustrates a larger

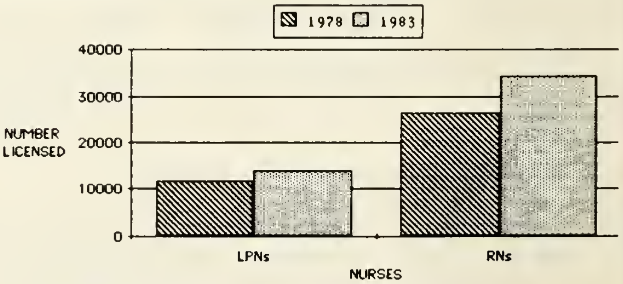

Figure 2. *North Carolina Nurses 1978 and 1983.*

From the Health Services Research Center, University of North Carolina, Chapel Hill 27514.

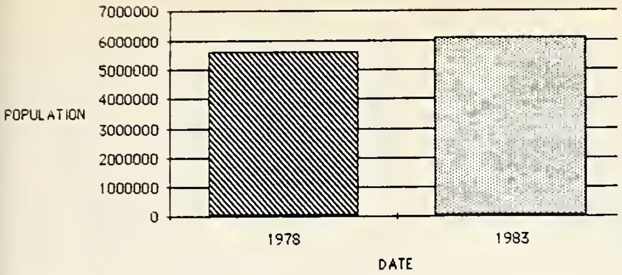

Figure 3. *Other North Carolina Health Professionals 1978 and 1983.*

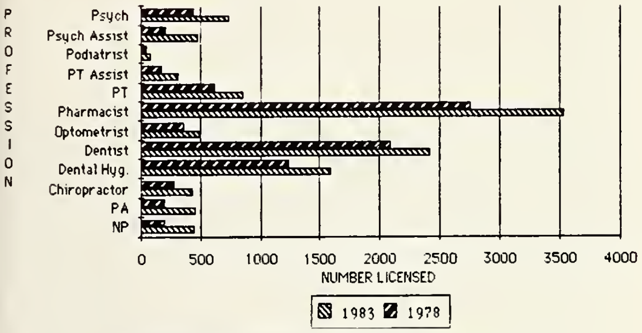

Figure 4. *North Carolina Population.*

increase in the number of registered nurses than licensed practical nurses, both numerically and proportionately.

Growth in the remaining health professions is shown in figure 3. By far the greatest proportional growth was in the ancillary professions. Nurse practitioners, physicians' assistants, and psychological associates[3] experienced growth in excess of 100 percent. Physical therapist assistants also experienced a proportionately large increase in their numbers (78.9 percent). While the increase in the number of dental hygienists was more modest (27.0 percent), it was proportionately greater than the increase in the number of dentists during the same period. Pharmacists were the largest group of licensed health professionals aside from nurses and doctors. Their numerical increase was large (778), but their proportional increase was a modest twenty-eight percent.

Finally, as shown in figure 4, the state's population increased by only nine percent from 1978 to 1983 so that the gain in numbers of health professionals represent real improvement in the supply of health care.

Notes

1. Health Services Research Center, University of North Carolina at Chapel Hill, Chase Hall 132-A, Chapel Hill, NC 27514, Telephone: 919-966-5011
2. American Medical Association: *Physician Characteristics and Distribution, 1982 Edition,* Chicago: Survey and Data Resources, American Medical Association. 1983.
3. Psychological associates are psychologists with a masters degree working under the supervision of a Ph.D. level practicing psychologist.

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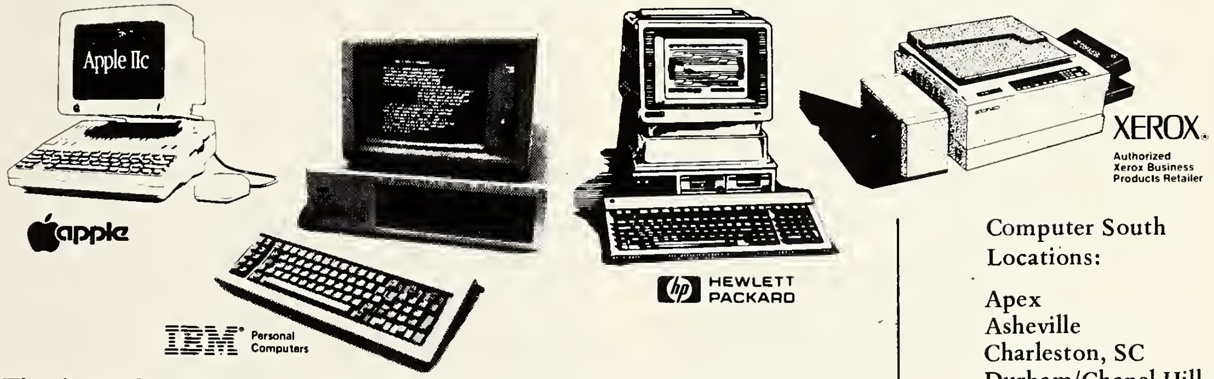

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In Vitro Fertilization at the North Carolina Memorial Hospital in Chapel Hill

Luther M. Talbert, M.D., Mary G. Hammond, M.D., Jouko Halme, M.D., Ph.D., Michael O'Rand, Ph.D.,
Carol Sloan, M.S. and Linda Bailey, R.N.

- *After two years the "test tube baby" program in Chapel Hill has an increasing success rate.*

In vitro fertilization and embryo transfer (IVF) consists of the aspiration of oocytes from the ovary by way of laparoscopy, fertilization with the husband's sperm, and transfer of embryos into the uterus after a suitable time interval. This paper is a report of the early experience with IVF at The North Carolina Memorial Hospital in Chapel Hill.

The first patient cared for in this program had laparoscopy carried out during February 1983. In that year, 41 patients initiated therapy with human menopausal gonadotropins and 38 underwent oocyte aspiration by laparoscopy. During 1984, 67 patients initiated treatment and 59 had oocyte aspiration carried out.

The protocols utilized at Chapel Hill are similar to those of the Jones Clinic at Norfolk, VA.[1, 2] Patients are accepted if they have irreparable tubal disease, endometriosis not responding to traditional treatment, unexplained infertility, oligospermia, antisperm antibodies, and multifactorial infertility.

All are seen for an initial evaluation by one of the authors (LMT). Screening laparoscopy is recommended in about 30% of patients to ascertain that a significant portion of at least one ovarian surface is visible for oocyte aspiration. At the time of screening laparoscopy vigorous efforts are made using scissor dissection to free up ovaries that are bound by adhesions. It is surprising how often ovaries that are completely covered with adhesions can be made visible by aggressive laparoscopic dissection. If sufficient ovarian surface cannot be brought into view by laparoscopy, patients are offered open laparotomy for this purpose so that the ovaries can be made available for later IVF.

Hyperstimulation aimed at the development of multiple follicles for aspiration is begun on day 3 of the menses. Our usual stimulation protocol consists of the administration of 2 ampules of human menopausal gonadotropins (hMG) daily until the serum estrogen level reaches 400 pg/ml and at least two follicles greater than 14 mm are visible by ultrasonography. Fifty hours after the last dose of hMG, 10,000 IU of human chorionic gonadotropin (hCG) is given, and laparoscopy is carried out 36 hours later. All visible follicles are aspirated and subjected to multiple washes. Follicular fluid and washes are transported to the adjacent laboratory and searched for oocytes using a dissecting microscope. Fertilization is carried out in Ham's F-10 solution with 7.5% fetal cord serum or preovulatory maternal serum. Fetal cord serum is always used when the female partner has been shown to have antisperm antibodies. After 16-18 hours in the insemination medium, the oocytes are transferred into growth medium consisting of Ham's F-10 solution with 15% serum added. Forty-four to seventy-two hours after insemination, all cleaved embryos are transferred into the uterus. The luteal phase is supported with 25 mg progesterone in oil intramuscularly daily and pregnancy testing is carried out 14 days after transfer. If the pregnancy test is positive, hydroxyprogesterone caproate (Delalutin) 250 mg weekly is administered until 20 weeks from transfer.

Results

During 1983, 41 patients were started on hMG stimulation. Three cycles were discontinued because of inadequate response, leaving 38 cycles which resulted in laparoscopy. Embryos were obtained in 27 patients (71%), but only one patient established a clinical pregnancy. This pregnancy resulted in a normal liveborn infant.

Because of the unsatisfactory pregnancy rate, the program was closed during November and December 1983. Clinical and laboratory protocols were carefully reviewed by the local staff and by outside consultants. Modifications were made to reduce the dose of hMG, and quality controls in the oocyte laboratory, already stringent, were made more rigid. The program was reopened in January 1984. Pregnancy rates were greatly improved during 1984. Three pregnancies conceived during 1984 have been delivered (1 with triplets) and others are ongoing. The pregnancy data for 1984 are given in table 1.

The pregnancy rate during 1984 was 14% per laparoscopy and 20% per transfer. Two spontaneous abortions occurred. Thus, a woman coming to laparoscopy during 1984 had an 11% probability to obtain a live birth. These data are consistent with results from the major national and international IVF clinics.

From the Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology and Department of Anatomy, University of North Carolina School of Medicine, Chapel Hill 27514.

Table 1
1984 IVF Data: The North Carolina Memorial Hospital

Started stimulation	67
Discontinued cycle	8
Laparoscopies	59
Transferred embryos	41
Pregnant	8

Discussion

The first human birth as a result of IVF occurred in 1978.[3] By 1982, the pregnancy rate per laparoscopy had risen to 12-15%, and the pregnancy rate per embryo transfer to 18-25%. Taking into account the spontaneous abortion rate, most successful clinics in the world now report that 10-15% of patients undergoing laparoscopy actually achieve a live birth.[1, 2, 4] The procedure, therefore, has become a viable option for treatment of infertility that has not responded to the usual methods of therapy. Although IVF was initially considered to be appropriate treatment only for patients with tubal disease, experience has shown that patients with endometriosis, unexplained infertility, and multiple factor infertility also respond well to this therapy. Indeed, IVF appears to be an effective therapy for male factor infertility, provided 250,000-500,000 sperm survive the washing procedures preparatory to IVF and provided the rate of motility is satisfactory. Pregnancy rates are somewhat reduced in this group.[5]

Appropriate referral of patients to a center for IVF requires an understanding of the concept of fecundability (likelihood of conception) after various treatment protocols have been carried out.[6, 7] Patients who undergo surgery for tubal disease or endometriosis and who do not conceive within 18-24 months are unlikely to do so and should be considered for IVF.[8] Secondary surgical procedures for either of the above result in approximately 10% pregnancy rates over the ensuing six years.[8] IVF is a less expensive and more effective treatment modality than is a second surgical procedure.

Indeed some patients with severe tubal or adhesive disease may be best served by direct referral for IVF. For example, patients with both proximal and distal tubal disease have a pregnancy rate after surgical therapy that approaches zero, and Hulka[9] has pointed out that in the presence of distal occlusion similar results are obtained when more than half of the ovarian surfaces are obscured by adhesive disease. These patients, therefore, might best be considered for IVF without an attempt at surgical correction. Patients with severe endometriosis and extensive adhesive disease respond poorly to surgical and/or medical treatment and might appropriately be considered for IVF if a total of one ovarian surface is visible at laparoscopy. Pregnancies are rare in patients with long-standing (5 years or more) infertility due to oligospermia or multiple factor infertility, and these patients likewise are appropriate candidates for IVF. Patients with unexplained infertility seem to respond well to IVF.[2] It is of importance that referral be made without undue delay, since the pregnancy rate in patients undergoing IVF appears to decline after age 40.

IVF and embryo transfer have had a major impact on the surgical management of benign diseases in the female pelvis. In the recent past, most gynecologists recommended hysterectomy when salpingectomy was required in patients with chronic pelvic inflammatory disease, a practice which is clearly in error in 1985 except in emergency circumstances. When the tubes must be removed in a young, especially nulliparous, woman, every effort should be made to preserve the uterus and all possible ovarian tissue for future IVF. Indeed, even if both tubes and ovaries must be removed, consideration should be given to salvaging the uterus, since at least two live births have been reported from cryopreserved donor embryos from unrelated couples.[10] With further improvements in the primary pregnancy rates and in cryopreservation techniques, donor embryos may become available to larger numbers of women.

The advent and rapid development of IVF and embryo transfer have had a major impact on the management of infertile couples and on the surgical management of benign pelvic abnormalities in young women. The impact of these techniques will become even more profound as pregnancy rates improve and as cryopreservation of human embryos becomes a more generally accepted reality.

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I requested the following information which I felt would make the paper more useful to doctor and patient:

1. Names and telephone numbers of persons in charge:	
Director, Luther M. Talbert, M.D.	*–966-5438*
Nurse Coordinator, Linda Bailey, R.N.	*–966-1150*
2. For new appointments	*–966-4459*

3. *Waiting time from the initial visit to a treatment cycle is three to six months.*
4. *Cost — The present charges for a cycle of IVF at NCMH is $3700.00. This is a comprehensive fee which covers both professional and hospital charges. Most patients are reimbursed for half or more of the cost of IVF by their respective insurance carriers. Indeed, some companies pay in full. Because of the great variation in the policies of various insurance policies, prospective patients should check with their own insurance carriers. If either the physician or the patient requires assistance in dealing with the insurance company, they may contact the clinic Financial Counselor, Ms. Rita Brantley at 966-2131.*

EAS

SCIENTIFIC ARTICLE

Provocative Exercise Testing: A New Role for Cardiac Rehabilitation

Charles L. Baird, Jr., M.D.

- *A study of 121 patients at the Virginia Heart Institute between 1976 and 1982.*

EXERCISE testing is widely accepted for diagnostic and prognostic purposes in the management of ischemic heart disease. However, its role in the serial evaluation of therapeutic intervention has been limited due to cost, inconvenience and the failure to appreciate the necessity for objective pharmacologic control of myocardial ischemia. The cardiac rehabilitation program at the Virginia Heart Institute was modified to include nursing-supervised provocative exercise testing as a method of selecting therapy. Those patients whose exercise-induced myocardial ischemia could not be reversed pharmacologically or whose exercise performances were complicated by fatigue, hypotension or drug intolerance were considered for surgical intervention. The experience of the Virginia Heart Institute from 1976 to 1982 and the provision of provocative exercise testing during a six-week cardiac rehabilitation program are presented.

Methods

Patients with angina pectoris referred to the Virginia Heart Institute for outpatient rehabilitation underwent risk stratification prior to entering the program utilizing noninvasive and invasive methodologies. Those patients with unstable angina, intractable arrhythmias, congestive heart failure or left main coronary artery disease were excluded.

The exercise laboratory consisted of four electrocardiographically monitored stations. The six week program consisted of three 30-minute exercise sessions per week and involved both upper and lower extremity exercise. The nursing-supervised graded exercise test was symptom limited and consisted of ten minute bicycle exercise periods with initially low work loads. The exercise test terminated if the patient developed severe chest discomfort, arrhythmias or hypotension. Blood pressure, pulse rate and double product were correlated with electrocardiographic changes at 0, 5 and 10 minutes of exercise and were recorded for comparative purposes.

Three initial periods were utilized to establish a data base prior to drug intervention. Drug titration was initiated generally with a single drug in order to obtain maximum response and to minimize spontaneous variability. Weekly staff conferences were held with the nursing staff to review the patients' responses to drug intervention during the periods of provocative exercise testing.

Results

One hundred and fifty patients underwent cardiac rehabilitation with provocative exercise testing between 1976 and 1982. This group included 127 patients with ischemic heart disease and 23 with non-ischemic heart disease. Outpatient cardiac catheterization using the Sones technique was performed on 95% of the patients with ischemic heart disease (121/127); 22% (5/23) of those patients with non-ischemic heart disease required cardiac catheterization for

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From the Virginia Heart Institute, Richmond, VA 23221.

Table 1
Patient Distribution

Ischemic Heart Disease	121 Patients	100%
Pre-event, angina without M.I.	70	58%
Angina post M.I.	25	21%
Angina post aorto-coronary bypass	10	8%
Post M.I.	7	6%
Post aorto-coronary bypass surgery	9	7%

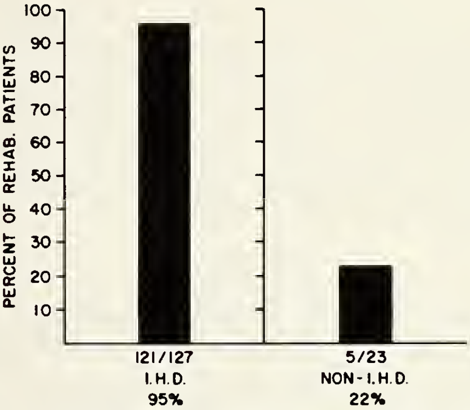

Figure 1. Catheterization procedures performed between 1976 and 1982 on Virginia Heart Institute rehabilitation patients. Patients with ischemic heart disease (I.H.D.) are on the left; non ischemic heart disease (NON-I.H.D.) are on the right.

further clarification (figure 1). Table 1 clinically classifies the 121 patients with ischemic heart disease.

Figure 2 provides the coronary angiographic data in patients with greater than 50% luminal narrowing.

Fifteen percent of our patients required surgery (18/121) at the end of the six-week program (figure 3). Three of these patients had single vessel disease, five had two vessel disease, and 10 had three vessel disease (figure 4). Medical management was considered successful in 85% (103/121) of the patients undergoing a drug intervention rehabilitation program.

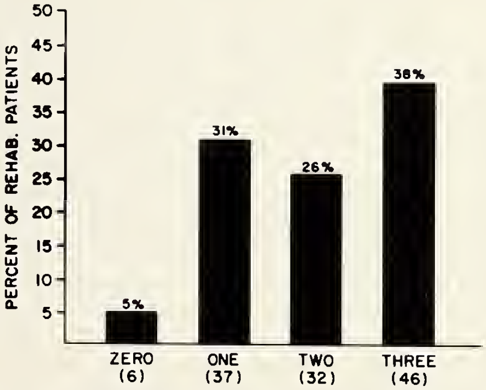

Figure 2. Distribution of coronary artery disease among 121 patients in the study. Six patients (5%) had no coronary artery disease; 37 (31%) had disease of one vessel; 32 (26%) had disease of two vessels; and 46 (38%) had disease of all three coronary arteries.

Discussion

The incorporation of provocative exercise testing into cardiac rehabilitation integrates monitored pharmacologic intervention into the accepted protocol of exercise therapy, psychosocial support and risk factor modification. This broadens the responsibility of cardiac rehabilitation and allows an active role for cardiac nurses in the application of drug therapy utilizing serial provocative exercise testing in the management of patients with ischemic heart disease who are potentially at high risk. The prognostic value of exercise testing in the prediction of survival in patients with coronary arterial disease has been previously documented.[1] Moreover, those patients who demonstrated reduced duration of exercise, hypotension or cardiac arrhythmias were identified as high risk for sudden death.[2]

Those patients who continued to exhibit exercise-induced myocardial ischemia unresponsive to maximal drug intervention or whose exercise periods were complicated by arrhythmias, hypotension or limited exercise performance were considered at increased risk and referred for surgical intervention. Conversely, those patients who demonstrated improvement during exercise testing were considered at low risk and advised to maintain medical intervention even when multi-vessel disease existed.

The recently published Coronary Artery Surgery Study demonstrated that the medical and surgical mortality rates were the same in a randomized study of 780 patients with stable angina pectoris.[3] This study supports the unreliability of coronary arteriography alone in providing a complete prognosis. The Virginia Heart Institute's retrospective analysis of 121 patients with ischemic heart disease further suggests a benign course even in those patients with three-vessel involvement (figure 3). Less than 20% of the patients evaluated at the Virginia Heart Institute failed to demonstrate reversibility of exercise-induced myocardial ischemia and were referred for myocardial revascularization.

Silent myocardial ischemia is responsible for 1200 unexpected sudden deaths daily in the United States. This problem led to the development of ambulatory cardiovascular

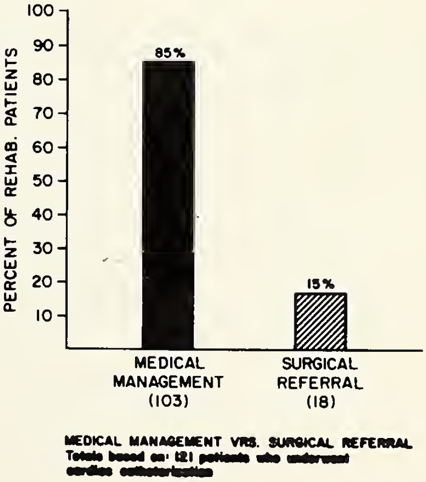

Figure 3. Eighteen patients (15%) were referred for surgical therapy; the remaining 103 (85%) were managed medically.

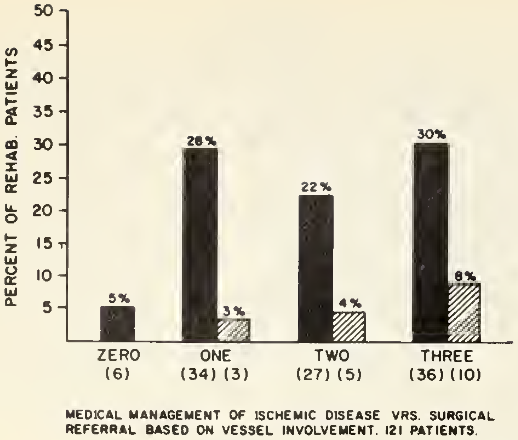

Figure 4. *Treatment choices in the 121 patients according to the number of coronary arteries involved in their disease. Among those referred for surgery (18), three had one vessel, five had two vessel, and ten had three vessel disease. Among those managed medically, six had no coronary arteries involved, 34 had one vessel, 27 had two vessel, and 36 had three vessel disease.*

screening with outpatient coronary arteriography at the Virginia Heart Institute in 1972.[4, 5] The recognition of significant coronary obstructive disease in a minimally symptomatic population led to the incorporation of drug intervention in the cardiac rehabilitation program which was initiated in 1976. The role of early detection at the Virginia Heart Institute is documented in this study since 58% of the patients entering the cardiac rehabilitation program had never experienced a myocardial infarction (table 1). The provocative exercise testing program not only affords the opportunity of selected treatment but also maximizes the use of risk factor modification, exercise conditioning and the drug stabilization which should be beneficial even in those patients referred for surgical intervention. The present epidemic of sudden death associated with multi-vessel disease, left ventricular dysfunction and complex ventricular arrhythmias has not been widely appreciated.[6] The continued reliance on subjective complaints by physicians tends to ignore the need for risk stratification based upon angiography and assessment of left ventricular function as well as arrhythmia analysis.

There is an urgent need to challenge the present health care system that has been unresponsive to the problem of sudden death. An alternative that deserves consideration is the development of ambulatory drug intervention interfaced with cardiac rehabilitation programs. Eventual acceptance by the medical community will require the recognition of serial exercise testing as a cost effective method of providing pharmacotherapy in the high risk population.

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TOXIC ENCOUNTERS

Aquarius Redux — Lysergic Acid Diethylamide

Ronald B. Mack, M.D.

• *In which "trip" is redefined, again. Caveat emptor.*

"WHEN the moon is in the seventh house and Jupiter aligns with Mars, then peace will guide the planet and love will steer the stars." Surely you remember this refrain from the ever-popular tune, "The Age of Aquarius," from the smash-hit stage sensation, "Hair." Seeing these words should bring back into consciousness the smell of incense, the turbulence between the youth and Establishment, the long hair, the "funny clothes," the "funny" cigarettes, miniskirts, and of course LSD — the drug of peace and love, brother. There is some evidence that there might be a resurgence of this rather "base" acid in this country among the incompletely formed in our culture — the adolescents. The use of LSD continues a decline noted three or four years ago but there are data to show that in some areas of America there has been a resurgence. In a recent statement the Drug Enforcement Agency alleges that a slight increase in the use of LSD is evident. It is always of interest to see our young people repudiate their parents' generation by emulating them as they were — my sons now have short haircuts and I do not; my boys wear three-piece suits and wing tip shoes to work and I don't. We do agree on at least one thing, however — LSD is a chemical trip that no one needs to take. The DEA alleges that the resurgence may be due to the fact that PCP (Angel dust) has such a bad reputation now that users are switching back to LSD.

LSD-25 remains the most potent and abused hallucinogen. Its discovery, as in so many medical breakthroughs, was by accident. Scientists in Switzerland were searching for pharmacologically useful products of ergot. Ergot is a fungus, a parasite of the rye grain. "Ergotism" has been known since the Middle Ages and the acquisition of this substance by the unwary produced convulsions and hallucination and was subsequently given the eponym St. Anthony's Fire. So here was this Swiss chemist in 1943 working with ergot alkaloids in the lysergic amide series who found that the 25th preparation (LSD-25), when ingested by the chemist, caused hallucinations.[1] It was even considered, during World War II, as a potential incapacitating agent in warfare. After WWII, LSD research was present in our country where supposedly it was used on emotionally ill patients in an effort to discern the biochemical nature, if any, of such illnesses. With the advent of strict Federal control, the use of LSD in such experiments dropped off remarkably.

From all of this followed the illicit use of this drug and the rest is history. Who can forget Timothy Leary, Ken Kesey, acid rock, *L*ucy in the *S*ky with *D*iamonds, etc.? What is it about this drug that so intrigues the user and makes "dropping acid" so cool? The users allege that at the very least LSD produces a "consciousness-expanding" experience, AKA a psychedelic experience. Of course there can be a wide variation in user response but a not unusual scenario goes something like this: initially, because LSD is rapidly absorbed from the GI tract, there can be noted, within 30-40 minutes of ingestion, marked mydriasis, conjunctival injection, salivation, cutaneous flushing, trembling, rapid pulse. (When was the last time you felt that way? When your secretary said that Mike Wallace and the 60 Minutes crew was in your waiting room?)

This initial, rather peculiar physical reaction is then followed by the real action, the "trip." Here the user feels depersonalized, with a loss of body image and decreased sense of reality. One of the most characteristic experiences reported by psychedelic drug users is the phenomenon of *synesthesia*, i.e., the translation of one sensory experience into another sense organ, e.g., "smelling" colors, "seeing" music — certainly, colors described as more vivid, and visual distortions with very altered perceptions of color, time and distance are typical. Hearing becomes very, very acute. Apparently external sounds such as music combine with the distorted imagery to enhance synesthesia. The sense of smell becomes remarkably intense and the presence of incense or flowers and music are part of the ritual.

The initial physical reaction lasts for a few hours whereas the psychic "trip" can last for 8 to 12 hours. At the peak of this psychedelic experience it is alleged that there is a feeling of rebirth and transcendence[1] — a feeling of oneness, compassion, tolerance and love for all things. After the peak is reached and the "tripper" re-enters, there is a gradual coming back to the "self" and to the environment. After such a voyage to unreality the passenger can recall details of the encounter. Now does that sound like a good time to you? Remember this is the desired effect; this is a good trip. The last time I felt this way was during a dream when I was called upon to do camp physicals on the Dallas Cowboy Cheerleaders. Some authors suggest that LSD affects the hypothalamus and therefore serotonin metabolism. Serotonin is supposedly one of the neurotransmitters that regulates or censors the flow of information transferred at nerve cell synapses. By blocking or antagonizing serotonin, LSD allows the "inner and outer world contents to stream into the brain."[1]

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

A "bad trip" can be scary indeed — it consists of an acute panic reaction with feelings of identity loss and/or a disintegration into nothingness or a feeling that there is no reality. The patient can have very frightening illusions or delusions with real honest-to-goodness marrow-shaking true hallucinations. "Bad trips" seem to be more common among neophyte experimenters and people who take very large doses of this delightful fungus derivative. If a preschool child gets into this stuff accidentally the situation may be hard to diagnose — be sure to include accidental LSD ingestion in your differential diagnosis of a severe, acute panic reaction (you mean like the three-year-old out there in the clinic today who was told that he needed some "shots" in order to get into nursery school and who got so "freaked out" that his screams shattered the glass on all the otoscopes and whose bouncing off the walls caused your diplomas to fall off the wall?). Prolonged psychotic behavior following LSD use can also occur and closely resembles paranoid schizophrenia. It should be mentioned that LSD can't be taken continuously and still reproduce its psychedelic potential day after day; tolerance develops quite quickly and in order to regain the possibility of having a pleasant voyage the serious traveler needs to abstain for at least a few days.

Some word should be mentioned about this drug's physical descriptions as found on the street. LSD is cheap to make but apparently it is most frequently imported from foreign "connections." The drug is available in capsules, as a powder, in solution, as a tablet on a piece of lump sugar, impregnated into gelatin squares (known as "window panes") or blotter paper (known as "blotter acid"). Recently I received the following notice from a nearby elementary school: "To All Concerned Parents With Unsuspecting Children: A form of tattoo called 'Blue Star' is readily available in some areas of the U.S. It is a small sheet of white paper containing 'blue stars' the size of pencil erasers. Each star is saturated with LSD. Absorption can occur through licking the star or just handling the paper. There are also brightly-colored tabs the size of postage stamps which have pictures of Superman, Mickey Mouse, other Disney characters, etc. and so on." Think of this: an ounce of uncut LSD can provide 150,000 "hits" of 200 μg each; 35 μg or more can cause "hallucinations" and the usual dose on the street is 150-200 μg. Apparently most LSD sold on the street is really LSD. However, it is alleged that a fair amount of LSD is laced with PCP. You can take LSD into your body any way you wish but per os is the usual way to go.

The treatment of LSD "intoxication" really is restricted to the unfortunate "acid-dropper" who undergoes a "bummer" (AKA "bad trip") — the acute panic reaction — or to an innocent pre-school or older victim who gets the drug by mistake. People on "good trips" generally do not come to visit you in the emergency room. It is usually too late to attempt gastrointestinal decontamination and of course there is no antidote. The essential treatment for a "bad trip" is to "talk him/her down," to establish for the patient the link to reality. To try to do this in a busy emergency room may not be a good idea for the presence of the white coats, other patients, telephones ringing, beepers going off, and the incessant noise often exacerbate the hallucinations. A quiet non-threatening room is more suitable whereby you can re-introduce to the patient the "real" world slowly and positively. Chlorpromazine (Thorazine) has been a time-honored suggestion for relief of the panic but this drug can cause hypotension and severe cardiovascular collapse and is best avoided. The benzodiazepines, e.g., diazepam, are preferred by many authorities as a safe, efficient therapeutic modality if you need to use a drug at all. Still, the essential treatment consists of a guide or leader to talk the patient back into the less weird world that we live in.

Currently I am working on a series of experiments in which I have discovered the presence of love receptors on the heart. I have named them *lambda* receptors. There are several types, such a lambda_1, lambda_2, etc. These love receptors can change frequently in response to many variables and, we have discovered, are in some ways age-dependent. For example in the first 6 months of life an infant only produces a limited supply of lambda receptors with agonists with a fairly long half-life (T½) and which are directed towards the self. At 6-8 months of age the infant also develops love receptors for its mother and if the mother leaves the child's visual presence for any period the infant cries and this is referred to as separation anxiety. The ramifications of these experiments seem almost limitless and I am grateful to my department chairman for his encouragement and help in obtaining a grant for this work.

Such examples of how love receptors function include: the people who fall in and out of love quickly have lambda_1 receptors with a very short T½; people who remain happily married for 40 or 50 years obviously have love receptors with a very long T½ and so on. Our work suggests, after meticulous experiments, that aphrodisiacs are probably lambda_2 agonists. (We have not found one yet that really works.) Other agonists, false transmitters actually, include perfume for women or aftershave lotion for men, money, fur coats, sumptuous meals, etc. Furthermore, we have discovered that certain human characteristics can reduce the T½ of these love receptors — examples include halitosis, love affairs outside of the current love relationship, persistent nocturnal headaches, etc. As you might imagine, congenital absence of a lambda receptor also occurs, often resulting in spinsterhood, bachelorhood, etc.

One exciting experiment, finished just this past month, demonstrates that love for a grandchild causes a remarkable increase in lambda_3 receptors with the longest half-lives discovered to date. We plan in the future to investigate lambda agonists that have even longer T½s and that are not dialyzable. There seem to be enough lambda blockers at this time.

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A Checklist of Practice Marketing Ideas

Leif C. Beck and Patricia M. Salmon

• A brief outline of ideas for marketing your practice.

ARTICLES on marketing tend to miss their mark when directed to practicing physicians. Many of the articles seem directed to broad principles which doctor-readers find just do not reach the realities of their practices. Others present so many self-evident points that they fail to give the physicians much to work with.

As consultants to medical practices, we recognize both the importance of the marketing topic and the difficulty in properly translating it for practitioners. Hence, this ''semi-outline'' is presented as a variation in form intended to help doctors to get hold of the ideas.

Marketing is an attempt to anticipate and/or shape consumer behavior. To do that effectively, a practice must determine what patients want or need as well as what motivates their choices in health care. It must then develop strategies and routines either to adapt the practice to the consumer's needs and/or expectations or to reeducate patients regarding health care choices. The goals would be to make the particular practice most appealing as a health care provider.

Though this is no easy task, it can be accomplished with careful analysis and planning, followed by a variety of specific steps. The process involves the following:

I. Practice Assessment

The obvious benefit of assessing a practice is to identify its pluses and minuses. Practice assessment, however, provides a variety of other benefits:

- It gives the practice an opportunity to lay the groundwork for developing marketing strategy.
- It provides the practice with direction and thus offers it an opportunity to shape its future rather than just letting it develop by chance.
- It helps the practice and its people use their time, resources and skills most efficiently and to their best advantages.
- It helps the practice deliver a better level of patient care.

There are two components of practice assessment: internal assessment and external assessment. Let us describe each.

A. Internal Assessment

(1) *Developing a patient profile.* To accomplish this, a practice must analyze its patient mix. This includes gathering information on those people (i.e., age, occupation, marital status, insurance coverage and the like) along with their opinions and attitudes on such matters as:

- Do the patients understand the specialty?
- What do they think of the physical facility?
- Are they satisfied with the health information they receive?
- Why are they seeking treatment?
- Do they want additional services that the practice does not provide?

This information can be obtained through fairly simple research and the use of patient questionnaires.

(2) *Assessing the staff.* This should include considering how an office's employees empathize with the patients. Do they understand this part of their job? How do they handle patients' questions as well as patients' complaints? Do they complement or detract from the doctor's or doctors' personalities and styles?

In advising physicians about marketing, we often point out that they should not spend much on marketing routines if their own ''house'' is not in order. Grumpy staff, long waits, constantly busy phone lines, unattractive offices and the like are all involved in patients' choices when seeking health care.

One obvious source of information about staff is careful observation. Additionally, patient questionnaires will often tell much about the quality and personality of an office's personnel.

Physicians should also pay close attention to patients' comments about the employees, even those seemingly said in jest. Those casual comments often say much more than we realize.

(3) *The self assessment.* The physician must put into writing some critical evaluations of himself or herself, and a group practice should do this for its physicians both individually and collectively. Important questions include:

- How does the physician rate his/her interpersonal skills?
- What are his/her major strengths or weaknesses as a physician?
- Is the doctor(s) satisfied with the type of patients being seen?

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From the Health Care Group, 400 GSB Building, Bala Cynwyd, PA 19004.

- Are there other types of patients he/she would prefer to see?
- What are the doctor's personal goals and ambitions?

(4) *Assessment of office facility*. This would include considering whether the waiting room and reception area are comfortable and clean. Does the practice offer areas of patient confidentiality for billing problems or surgical scheduling? Does the facility reflect positively on the practice? Does it project the image the physician(s) desire? Is it accessible and easy to find?

Again, these items can be considered through observation as well as through solicited or unsolicited patient comments and patient questionnaires.

(5) *Assessment of the practice's clinical services*. This would include whether the range of services offered is compatible with specialty type; are there other services that could be provided to improve the practice? What would be the cost of adding these services, and would they be useful to the patients and profitable to the practice?

B. External Assessment.

(1) *Assessment of competition*. It is important to identify a practice's "competitors." What does the doctor know about them? Is the practice losing patients to them? Is it gaining patients from them? Is the competition increasing, decreasing or stable?

Information on other practices, though partly known just by involvement, can also be obtained through the Yellow Pages, patient surveys, ex-patient surveys, pharmaceutical representatives and the like.

(2) *Assessment of demographics*. This includes considering the service area's breakdown by age, sex, race, household size and so forth. Is the service area's population increasing or decreasing? Are there any important changes taking place in the area demographics?

Not every marketing idea works for the entire population. On the basis of demographics, a doctor might thus want to identify certain target areas with the most potential for successfully implementing its goals. As an oversimplified example, a geriatric practice would probably not seek out an area where the average age is 26, where the elementary school system has shown significant growth, etc.

(3) *Assessment of local business and economic environment*. What are the trends in employment? What types of businesses are moving into the practice area and the surrounding communities? Are there any newly developing plans as to local transportation, public utilities, zoning changes and the like?

(4) *Assessment of area's epidemiological environment*. This might include identifying the frequencies of disease and illnesses in the service area. Are there any concentrations of industry in the area that might contribute to the incidence of certain diseases or illnesses?

(5) *Assessment of social/cultural and legal/technological trends*. How might these affect the practice's future?

Much like internal assessment, the external assessment provides a means of identifying potential opportunities, needs and constraints. Both processes are a key part in developing the practice's objectives and adopting a business plan.

II. Developing a Business/Marketing Plan

With the supply and demand for health care providers radically changing, doctors should be aware of the changes and the long and short range effects on their practices. Mapping long and short term goals and constantly monitoring progress toward them will give doctors the best opportunity to accomplish the goals.

A business/marketing plan is a practice blueprint for the future. It allows a doctor to logically decide how he will in the future most satisfactorily provide his or her services and to efficiently allocate resources to accomplish those goals.

Suppose, for example, a cardiologist is in an area where the number of cardiologists is greater than can realistically be supported by the patient volume. It is thus essential that this doctor identify what he can offer to patients as well as what potential patients he should offer it to in order to make his practice different and more attractive than the others in the area.

Assessing the practice internally and externally, taking advantage of the strengths and eliminating or covering up the weaknesses and knowing and attempting to reach the largest potential patient population would help his practice compete well. In fact, real application to the effort could even put him in position to be a "premier" practice.

Once this doctor has determined his preliminary goals and objectives, studied and analyzed the local demographic statistics and trends, studied and analyzed the competition, evaluated his strengths and weaknesses, identified some opportunities on which to capitalize, he should have his plan in writing to act as a roadmap for the months and years ahead.

III. Marketing/Promotion Ideas

Once one had developed the plan, there may be many steps directed to actually reaching out to existing and potential patients. Without extending to the more "progressive" plays such as advertising, here is a list of steps to consider:

- Non-traditional office hours, such as evenings, mornings and/or weekends. Depending upon the age of one's patient population, patients may either be working or in need of rides that are more easily obtainable at less traditional times.
- Add additional services that allow the practice to offer "one-stop shopping," so to speak. For our cardiologist example, this might include stress testing, cardiac rehabilitation programs and nutrition counseling in his own facility for cardiac patients.
- A physician with an elderly patient population might consider assigning one person in his or her office to spend time "training" patients about their Medicare claims and how they should file them (depending upon the practice's policy under the new fee freeze). It is often particularly confusing for some senior citizens, and they tend to appreciate any help offices can give. Small brochures about the steps involved in filing Medicare forms for reimbursement are also popular.
- Depending upon the area's demographics, a physician might consider opening a satellite office to target another part of the area not now serviced by his colleagues. This doctor's accessibility might cause that area's patients to

start visiting him.

- Patient education information is important for any practice. Though it might be available through professional societies and/or drug companies, having it personalized with the practice's name is both a valuable marketing tool and a service to the patient.
- If the practice does not have one already, it should develop a Patient Information Booklet to provide a handy reference as to office policies and procedures. While usually helping save staff time, it is an excellent marketing tool as patients pass it on to friends.
- The use of patient newsletters is also an excellent marketing, as well as educational, tool. We see a wide variety of such newsletters with news about practice and patient activities, health informational columns, etc. A newsletter provides a service to patients while spreading the doctor's name and reputation.
- Involvement in community activities, such as lectures to senior citizens and other groups, is a traditional way for physicians to get their names out. It is still among the most successful practice-builders.
- Involvement with local industry might target larger blocks of patients, especially if contract relations with some employers can be worked out.
- Letters to referring doctors following patient visits are frequently taken for granted, but they are necessary marketing tools. A "marketing-oriented" doctor will handle the reporting obligation with special attention to the referrer's satisfaction.
- And some specialists send their referring doctors monthly or quarterly letters updating them on new findings in the specialty, new services available and whatever else will remind those referrers of the senders.

IV. Conclusion

We hope this low key discussion of marketing ideas as they might apply to a practicing physician will be useful. By reviewing our casual outline as though it were a checklist, those ideas might have more chance of actually being pursued than is typically the case.

LEARNING EXPERIENCES FROM UNC

Lest We Forget — Spring Is Here: North Carolina Spotless Fever in Adults

William B. Blythe, M.D.

SUMMER is coming, and Variety Vacationland once again will be alive with an abundance of outdoor activities: camping, hiking, strolling, and frolicking in the woods; gardening; picnicking; barbecuing under the trees; and lolling on the lawn.

Ah, Summer!

But wait! All is not sweetness and fun. The wood tick and dog tick, of which 3-5% are carrying Rickettsia Rickettsii, will also be aestivating outdoors among us. Thus, the specter of Rocky Mountain Spotted Fever will be hovering over the good physicians, reminding them that this disease is most prevalent in North Carolina from April through October.

Recently, Dr. Janet Fischer, a keen observer of Rocky Mountain Spotted Fever in North Carolina for over three decades, suggested at Pearls Day in Chapel Hill that North Carolina Spotless Fever may be a more appropriate name for Rocky Mountain Spotted Fever in *adults*.

This is her reasoning: approximately 64% of adult patients with Rocky Mountain Fever who do not demonstrate the much-emphasized rash die in spite of the availability of effective therapy and the fact that treatment on or before the fifth day of clinical disease almost always results in recovery. This appalling death rate in rash-free adults is a consequence of the physician not considering the correct diagnosis early enough.

It is Dr. Fischer's belief that this occurs largely because of two factors: 1) The adjective "spotted" is misleading. About 10% of adults never develop a rash and, in 20% more, the rash does not develop until the second week of the disease when complications and death are more apt to occur. 2) "Rocky Mountain" is also a misnomer and tends to obscure the fact that more cases of Rocky Mountain Spotted Fever are reported annually in North Carolina than any other state.

The only part of the name that accurately portrays the disease in adults in North Carolina is "fever."

Dr. Fischer advocates that a five-day course of tetracycline be strongly considered by physicians when confronted by an adult patient with the following:

From the Division of Nephrology, Old Clinic Building 226H, UNC, Chapel Hill 27514.

Camping, hiking, frolicking in the woods, picnicking, lolling on the lawn: beware the ticks.

1) an illness lasting for more than three days and getting worse.
2) a normal white blood cell count with a shift to the left in the differential count.
3) a severe headache.
4) *evening* fever greater than 102°. (The temperature is frequently normal when the patient visits the physician.)
5) Thrombocytopenia.

Keep North Carolina Spotless Fever in mind this summer.

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VELOSEF® CAPSULES
Cephradine Capsules USP

VELOSEF® FOR ORAL SUSPENSION
Cephradine for Oral Suspension USP

DESCRIPTION: Velosef '250' Capsules and Velosef '500' Capsules (Cephradine Capsules USP) provide 250 mg and 500 mg cephradine, respectively, per capsule. Velosef '125' for Oral Suspension and Velosef '250' for Oral Suspension (Cephradine for Oral Suspension USP) after constitution provide 125 and 250 mg cephradine, respectively, per 5 ml teaspoonful.

INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli, P. mirabilis, Klebsiella* species, and enterococci (*S. faecalis*).

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

Other antibacterial agents — Bacteriostats may interfere with the bactericidal action of cephalosporins in acute infection; other agents, e.g., aminoglycosides, colistin, polymyxins, vancomycin, may increase the possibility of nephrotoxicity.

Can two really equal four?

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Drug/Laboratory Test Interactions: After treatment with cephradine, a false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®. False-positive Coombs test results may occur in newborns whose mothers received a cephalosporin prior to delivery. Cephalosporins have been reported to cause false-positive reactions in tests for urinary proteins which use sulfosalicylic acid, false elevations of urinary 17-ketosteroid values, and prolonged prothrombin times.

Carcinogenesis, Mutagenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential or mutagenesis.

Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 4 times the maximum indicated human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cephradine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers: Since cephradine is excreted in breast milk during lactation, exercise caution when administering cephradine to a nursing woman.

Pediatric Use: Adequate information is unavailable on the efficacy of b.i.d. regimens in children under nine months of age.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported following use of cephradine: G.I. — Symptoms of pseudomembranous colitis can appear during antibiotic therapy; nausea and vomiting have been reported rarely. Skin and Hypersensitivity Reactions — mild urticaria or skin rash, pruritus, joint pains. Hematologic — mild transient eosinophilia, leukopenia and neutropenia. Liver — transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage. Renal — transitory rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others — dizziness, tightness in the chest, and candidal vaginitis.

DOSAGE: Adults — For respiratory tract infections (other than lobar pneumonia) and skin and skin structure infections: 250 mg q. 6 h or 500 mg q. 12 h. For lobar pneumonia: 500 mg q. 6 h or 1 g q. 12 h. For uncomplicated urinary tract infections: 500 mg q. 12 h; for more serious UTI, including prostatitis, 500 mg q. 6 h or 1 g q. 12 h. Severe or chronic infections may require larger doses (up to 1 g q. 6 h). For dosage recommendations in patients with impaired renal function, consult package insert.

Children over 9 months of age — 25 to 50 mg/kg/day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae*: 75 to 100 mg/kg/day in equally divided doses q. 6 or 12 h but not to exceed 4 g/day. Dosage for children should not exceed dosage recommended for adults. There are no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

For full prescribing information, consult package insert.

HOW SUPPLIED: 250 mg and 500 mg capsules in bottles of 24 and 100 and Unimatic® unit-dose packs of 100. 125 mg and 250 mg for oral suspension in bottles of 100 ml and 200 ml.

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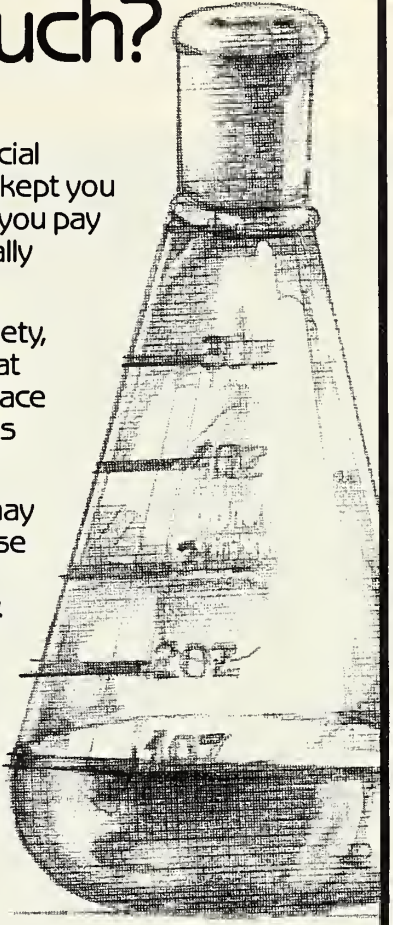

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Hospital Administrator: Harold Small

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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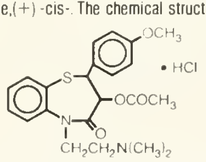
DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect, cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3 asthenia (1.2%), AV block (1.1%). In addition, the following eve were reported infrequently (less than 1%) with the order of presen tion corresponding to the relative frequency of occurrence.

Cardiovascular	Flushing, arrhythmia, hypotension, bradyc dia, palpitations, congestive heart failu syncope.
Nervous System	Paresthesia, nervousness, somnolen tremor, insomnia, hallucinations, and amnes
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiti mild elevations of alkaline phosphatase, SG SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitiv
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes vasospastic angina developed periods of transient asymptoma asystole approximately five hours after receiving a single 60- dose of CARDIZEM.

The following postmarketing events have been reported inf quently in patients receiving CARDIZEM: erythema multiforme; le kopenia; and extreme elevations of alkaline phosphatase, SG SGPT, LDH, and CPK. However, a definitive cause and effect betwe these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limite Single oral doses of 300 mg of CARDIZEM have been well tolerat by healthy volunteers. In the event of overdosage or exaggerat response, appropriate supportive measures should be employed addition to gastric lavage. The following measures may be considere

Bradycardia	Administer atropine (0.60 to 1.0 mg). If the is no response to vagal blockade, adminis isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed hig degree AV block should be treated with c diac pacing.
Cardiac Failure	Administer inotropic agents (isoproteren dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterer bitartrate).

Actual treatment and dosage should depend on the severity of t clinical situation and the judgment and experience of the treati physician.

The oral/LD$_{50}$'s in mice and rats range from 415 to 740 mg/ and from 560 to 810 mg/kg, respectively. The intravenous LD$_{50}$'s these species were 60 and 38 mg/kg, respectively. The oral LD$_{50}$ dogs is considered to be in excess of 50 mg/kg, while lethality w seen in monkeys at 360 mg/kg. The toxic dose in man is not know but blood levels in excess of 800 ng/ml have not been associat with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Cor nary Artery Disease or Angina Pectoris at Rest Due to Cor nary Artery Spasm. Dosage must be adjusted to each patient needs. Starting with 30 mg four times daily, before meals and bedtime, dosage should be increased gradually (given in divid doses three or four times daily) at one- to two-day intervals un optimum response is obtained. Although individual patients m respond to any dosage level, the average optimum dosage ran appears to be 180 to 240 mg/day. There are no available data concer ing dosage requirements in patients with impaired renal or hepa function. If the drug must be used in such patients, titration should carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acu anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safe coadministered with short- and long-acting nitrates, but the have been no controlled studies to evaluate the antiangin effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NI 0088-1771-47) and in Unit Dose Identification Paks of 100 (NI 0088-1771-49). Each green tablet is engraved with MARION on o side and 1771 engraved on the other. CARDIZEM 60-mg scor tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in U Dose Identification Paks of 100 (NDC 0088-1772-49). Each yell tablet is engraved with MARION on one side and 1772 on the oth

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North Carolina Medical Journal

Features for Patients June 1985

The Impact of AIDS on Blood Donation

Jerry E. Squires, Ph.D., M.D.

In 1978 and 1979 several hospitals in New York and Los Angeles recognized a syndrome of opportunistic infections in previously healthy young adult patients. The infections most frequently noted included Pneumocystic pneumonia, Candida esophagitis, disseminated cytomegalovirus and disseminated *Myocobacterium avium-intracellulare*. Epidemiologic investigation of these patients revealed that almost all were male homosexuals or bisexuals or parenteral drug abusers. At about the same time a similar population of previously healthy young men were recognized who developed an unusually aggressive form of Kaposi's sarcoma. Prior to this time Kaposi's sarcoma was most commonly described as a relatively slow-growing, locally invasive neoplasm of elderly men. The more aggressive form had been seen only in certain immunodeficient patients.

Laboratory evaluation of these patients demonstrated a profound defect in cell-mediated immunity accompanied by a relatively intact humoral immunity. The impaired cellular immune function was manifest in several ways, including: (1) anergy (lack of response) to multiple skin test challenges with antigens such as Candida, mumps, tetanus, etc., (2) lymphopenia (decreased proportion of lymphocytes in the blood), with many patients having fewer than 500 lymphocytes/mm,^{3} (3) decreased numbers of T-lymphocytes while numbers of B-lymphocytes were relatively normal, and (4) a severe deficiency of "helper" cells and an increased number of "suppressor" cells.

Since 1978 additional patients have been described who demonstrate the combination of opportunistic infections, Kaposi's sarcoma, an acquired severe deficiency of the cellular immune system and a lifestyle including homosexuality, bisexuality, or intravenous drug abuse. The term acquired immune deficiency syndrome (AIDS) has been most commonly applied to this complex of findings.

Early studies of large numbers of patients suggested that AIDS was most commonly transmitted through intimate sexual contact. However, the presence of AIDS in intravenous drug abusers initially suggested that an infectious agent might be transmitted parenterally (by injection). Subsequent documentation of AIDS in hemophiliacs as well as both adult and pediatric patients receiving blood transfusions have confirmed this mode of transmission. As cases have accumulated during the past four years, relatively well defined risk groups have emerged. As of February 1985, 8495 cases of AIDS have been recorded by the Centers for Disease Control (CDC). Of these, 73% have been homosexual or bisexual men; an additional 17% are intravenous drug users. Only 1% (approximately 100 cases) have been attributed to blood transfusion.

In spite of what appeared to be a relatively small risk of developing AIDS following a blood transfusion, public anxiety about the safety of the blood supply demanded that additional precautions be taken. Therefore, in March 1983, the U. S. Public Health Service issued a recommendation that members of groups at increased risk for AIDS should refrain from donating blood. In addition, the Food and Drug Administration recommended that all blood banks provide educational materials about AIDS to donors, and alter the medical history taken on each donor to include questions concerning AIDS symptoms, such as night sweats, un-

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From the Carolinas Region, American Red Cross, 2425 Park Road, Charlotte 28236.

explained fevers, unexpected weight loss, lymphadenopathy, and skin lesions. The effectiveness of these "interim guidelines" in reducing the risk of contracting AIDS following a blood transfusion is difficult to assess. It is important to realize, however, that during the past four years, while approximately 13 million patients received nearly 36 million units of blood and components, only 100 cases of post-transfusion AIDS have been reported.

In spite of the minimal risk of contracting AIDS through blood transfusion, public concern for the safety of the blood supply has been high, and a variety of demands have been placed upon the blood delivery system. One of the most complex of these was the question of **directed donations.** A directed donation is one in which the potential blood recipient selects his own blood donors from family, friends, co-workers or private donor clubs. Most blood donor centers have recommended that such directed donor programs not be established. The reason for the reluctance on the part of blood donor establishments to accept directed donations stems from two concerns: (1) the probable impairment of the volunteer donor system if large numbers of donors opt to withhold blood donation pending the need of a friend or family member, and (2) the probability that directed donations are actually *less* safe than the current voluntarily donated blood supply. The reason that these donations may, in fact, provide a less safe transfusion product results from the "social pressure" to donate blood for a friend or family member in spite of past medical history or lifestyle.

Another demand placed on blood banks due to the anxiety about AIDS resulted from a decrease in the numbers of potential donors. Some potential blood donors have been clearly confused by reports in the media. In a survey completed in 1983, 26% of 2000 adults polled nationwide believed that AIDS could be contracted by donating blood. This is clearly incorrect; nevertheless, the impact upon the blood supply in some areas of the country was significant.

The announcement in April 1984, that Dr. Robert Gallo of the National Cancer Institute had identified the probable cause of AIDS created new demands on blood banks. The virus implicated as the cause of AIDS is known as human T-lymphotropic virus-type III (HTLV-III). The association of this virus with the clinical syndrome of AIDS has, to some degree, been circumstantial, but the data are quite convincing. Evidence of the presence of HTLV-III was found in more than 90% of patients with AIDS; in addition, Gallo reported that each of ten blood donors whose recipients developed AIDS were found to have evidence of HTLV-III. Finally, chimpanzees experimentally infected with the HTLV-III virus developed enlarged lymph nodes similar to the lymphadenopathy that often precedes AIDS.

The development of a sensitive screening test for HTLV-III has been a major priority during the past year. Five companies were authorized by the Food and Drug Administration to adapt a test for antibodies to HTLV-III originally developed by the National Cancer Institute. The test itself is an enzyme-linked immunosorbent assay (ELISA) which uses viral antigens derived from whole disrupted HTLV-III. Antibody to HTLV-III has been found in 68-100% of patients with AIDS and in 84-100% of persons with an AIDS-related condition such as unexplained lymphadenopathy. On the other hand, fewer than 0.5% of individuals with no known risk for AIDS are reactive in the test for antibodies to HTLV-III. The sensitivity of the test has recently been reported to be greater than 96% while the specificity is generally considered to be greater than 97%.

The use of this ELISA test to screen donated blood for antibodies to HTLV-III should have been fully operational in most blood donor centers before May 1, 1985. At that time a variety of Public Health Service recommendations concerning the testing for antibodies to HTLV-III took effect. These recommendations affect the blood recipient, donor, and his physician in various ways.

The first of these recommendations suggests that all blood or plasma should be tested for HTLV-III antibody by the ELISA test and any found positive should be discarded. Clearly, the major impact of this recommendation will be upon the potential blood recipient. While the risk of acquiring AIDS through blood transfusion has been minimal, the use of this test should reduce that risk still further. Hopefully, this will restore the confidence of many potential blood recipients in the safety of the blood supply. The Public Health Service also recommends that potential blood donors be informed that their blood will be tested for antibody to HTLV-III. This notification should have begun on or about May 1, 1985. The impact of this notification on the willingness of donors to continue to donate is difficult to assess.

One of the most difficult recommendations concerns notifying donors who have positive tests for antibody to HTLV-III. While there is great concern about the psychological impact of this information, failure to provide the patient with such notification might inappropriately preclude medical evaluation and protection of sexual contacts. It will be imperative to make the patient aware that the significance of a positive test for antibodies to HTLV-III is uncertain. The limited information available on the natural history of the syndrome suggests that only 5-19% of seropositive homosexual men develop AIDS within 2-5 years; an additional 25% develop lymphadenopathy, oral candidiosis or other AIDS-associated condition. In an effort to minimize the risk of reporting false-positive results to the individual, each initially positive result will be repeated in duplicate; any repeatedly positive sample will also be submitted for confirmation testing. Currently, the confirmation test most commonly used is the

Western blot. The numbers of blood donors who will have confirmed positive test results is difficult to estimate. However, preliminary evaluation suggests that fewer than 0.03% of the donor population will have confirmed tests for antibody to HTLV-III.

Those few blood donors who are identified by the testing procedures will be contacted by a Red Cross physician or by a trained nurse and referred to appropriate doctors or clinics. Perhaps a more tangible concern is that members of certain groups at increased risk for AIDS will donate blood simply to determine if they carry the antibody to HTLV-III. The Public Health Service is handling this portion of the problem. Its program is described in some detail in the papers that follow.

AIDS Hotline
1/800/225-AIDS

AIDS Information for Doctors and Patients

J. N. MacCormack, M.D.

Alternate Sites for HTLV-III Antibody Testing

On March 2, 1985, Margaret Heckler, Secretary of Health and Human Services, announced that the FDA licensed the first commercial manufacturer to make and distribute test kits for the detection of antibodies to the HTLV-III virus. This has already been widely reported in the press. Blood banks have begun proficiency testing. During May, blood banks are expected to begin donor notification of test results. The State Laboratory is expected to have the kits available to begin performing the HTLV-III antibody test sometime in early May. The anticipated public health benefit of this overall program to protect the nation's blood supply has dictated the unusually rapid introduction of this test.

Alternate test sites will be necessary to discourage high-risk individuals such as male homosexuals and intravenous drug abusers from using the blood banks simply to be tested. Although the test is highly specific, there is the danger that some persons will have negative tests but harbor the virus, thereby allowing a donor to contaminate the blood supply. Local health departments will serve as alternate test sites for HTLV-III antibody testing, which will contribute to the goal of protecting our blood supply. None of us welcome the prospect of needing a transfusion, but the possibility becomes a greater concern unless everything possible has been done to insure the safety of that product.

Local health departments that became alternate test sites are expected to provide pre-test counseling, to draw and submit serum samples to the State Laboratory, and to conduct post-test counseling. The Sexually Transmitted Disease (STD) Branch will assist local health departments in establishing alternate test sites.

Local health department staff may not have the time or be able to answer all questions concerning HTLV-III antibody testing. In early May, the STD Control Program will install a toll-free Hotline (1-800-225-AIDS) to assist in answering questions or making referrals to support groups. Community mental health centers have been informed that local health departments may be referring individuals with positive test results.

General Guidelines for Alternate Test Sites

A. General responsibilities

1. *Provide pre-test counseling.* All patients should receive a "Pre-Test Information Sheet"; this should be discussed with the patient (see protocol for pre-test counseling).
2. *Draw serum and send to State Laboratory.* The State Laboratory protocol for specimen collection should be followed.
3. *Provide post-test counseling.* Patients with positive test results should be given the information sheet entitled "Information for those with a Positive HTLV-III Antibody Test." This should be reviewed with patient.

B. Availability of sites and scheduling

1. If a county health department has satellite clinics, it may be easier to decide to offer HTLV-III antibody tests at only one center. If more than one site will be used, inform the STD Control Program so that pre-numbered labels for additional sites can be provided.
2. Some health departments may decide to offer testing only during their STD clinic sessions, while others may offer the testing at other specified times or at any time. Each health department should decide how to schedule availability of testing.

C. Who to test

1. Those requesting a test will have different reasons for doing so:
    a. Member of a high-risk group, e.g., homosexual, bisexual, intravenous drug abuser
    b. Recent recipient of a transfusion
    c. Recent positive HTLV-III antibody test, e.g. at a blood bank
    d. "Worried-well," e.g., one gay encounter years ago
2. Those who have recently had a positive antibody test should not be retested. They should be referred to their personal physician for medical evaluation; an additional test will not provide them with any additional information *without* a medical evaluation. Although the Red Cross will not be referring any positives to the health department, some of those individuals may request an additional test at the health depart-

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From the Epidemiology Section, Division of Health Services, Department of Human Resources, Box 2091, Raleigh 27602-2091.

ment. Individuals with positive tests should not be retested by the health department for at least six months from the date of their initial positive test.

D. Confidentiality/record keeping/ reports

1. Testing will be anonymous. Even though an individual may be known at the health department, the patient's test results should not be posted to any record with his/ her name.
2. Those tested will be given a card with a code number which will be used on the lab requisition form and specimen. Pre-numbered labels will be provided by the STD Branch. The patient must return with this card to be given test results.
3. A very simple record of those tested will be maintained on a log sheet with numbers corresponding to the pre-numbered labels. The following information should be documented on this log sheet: the date tested, the date results returned from the lab, the test results, and date post-test counseled. If a person was only counseled and not tested, the date of the counseling session should be recorded on the bottom of the log sheet.
4. The only report requested is a copy of the log sheet of those tested. This should be sent to the STD Program Regional Office 15 days after the end of the testing month.

Specimen Collection Protocol

The N. C. State Laboratory of Public Health will accept human sera from patients of Local Health Departments for the detection of antibody to HTLV-III. Specimen collection and transport kits for HTLV-III antibody are available free of charge to Local Health Departments by writing or calling the State Laboratory Mailroom, P.O. Box 28047, Raleigh, N.C. 27611, telephone: (919) 733-7656.

Specimen collection

1. Aseptically collect a blood sample into a 7 mL sterile red top vacuum tube.
2. Allow the blood to clot.
3. Centrifuge the blood at 2000-3500 rpm's for 10 minutes.
4. Transfer the serum into the plastic screw cap vial provided in the specimen transport mailer.
5. Removal of the serum from the clot as soon as possible reduces hemolysis.
6. A minimum of 2 mL of serum is required.

Labeling specimen and DHS form 1424

Five duplicate prenumbered labels are provided for each specimen and corresponding records. The form to use for submitting serum for this test is DHS 1424, Viral Culture and Non-Syphilis Serology. Labels should be affixed as follows:

1. Tube of blood.
2. Plastic serum transport vial.
3. Patient code card.
4. First and second copy of DHS Form 1424 in the area marked "patient name."

Completion of DHS form 1424

1. Write or stamp the return address of the county on both copies of DHS Form 1424.
2. In the area marked "Specific Agent(s) or Disease Suspected" write HTLV-III Antibody.
3. Fill in the collection date, and the age, race and sex of the patient.
4. No other test will be performed on this specimen except the HTLV-III antibody test(s).

Specimen transport

1. Insert the labeled vial of serum into the plastic bag provided.
2. Wrap the completed DHS Form 1424 and the cardboard insert around the bag with vial.
3. Place this into a non-syphilis serology mailer with a blue tape band.
4. Stamp the health department return address on the outside of the mailer and submit to the Laboratory.

If you are notified by the State Laboratory that the specimen was unsatisfactory for any reason, recollect the specimen when the patient returns for the results. Assign a new patient code number. Do not reuse previously assigned number. Technical questions should be addressed to the Virology and Serology Branch, State Laboratory of Public Health, P.O. Box 28047, Raleigh, N.C. 27611. Telephone: 919/733-7544.

Protocol For Pre-Test Counseling

Those individuals inquiring about or requesting the HTLV-III antibody test will have their own particular expectations of what information the test will provide. This test will probably not fulfill all of their expectations. Without a basic understanding of what information this test can or cannot provide, they could easily be misled by the test results. They should be prepared to deal with the ambiguity of the results and the possible social repercussions of this test.

The purpose of pre-test counseling, then, is to provide the individual seeking the antibody test with enough information to make an informed decision. To achieve this, the counselor should review the "Pre-Test Information Sheet" with the patient. Only through interaction with the patient can the counselor feel relatively confident that the patient will make an informed decision whether or not to have this test.

A counselor could easily spend thirty minutes or more in pre-test couseling. In a busy clinic, only five minutes may be available. Since time will be a major problem, the counselor should focus only on the essential points while reviewing the "Pre-Test Information Sheet" with the patient.

Those individuals selected to provide counseling should understand some basic facts about HTLV-III antibody testing:

1. The test is of very limited diagnostic value. It is designed to detect antibodies to the virus thought to cause AIDS. Its intended use is to screen blood to protect the nation's blood supply.
2. A positive test most likely means that an individual has been **exposed** to the virus and produced antibodies. It does **NOT** mean that he has AIDS or will develop AIDS.
3. The individual *could* be infectious, so precautions should be taken not to spread the virus.
4. At present, viral isolation can only be performed in sophisticated research labs.
5. False negatives are possible, especially in high risk individuals (homosexuals and intravenous drug abusers).
6. False positives are more likely to be seen in individuals at low risk. All patients with positive results need to consult their personal physicians for medical evaluation.

Outline for Pre-Test Counseling

1. Reason for exam

Many people may begin by simply asking if they can have a test for AIDS. Ask why they want to have the test. Briefly explain that those in high risk groups (homosexuals/intravenous drug abusers) should already be following prevention recommendations not to donate blood and to engage only in "safe sex," i.e. using a condom. Let them know that this is *NOT* a test for AIDS. Consider following the outline below.

2. Four major points

Using the "Pre-Test Information Sheet," stress the following points:

a. **This is not a test for AIDS.** This is a screening test to protect the nation's blood supply. At this point in time, we do not fully know the implications of a positive or negative test.

b. **A positive test** does not mean one has or will develop AIDS.

c. **A negative test,** especially in high risk individuals, does not necessarily mean one does not have or will not develop AIDS (explain high risk if this has not previously been discussed).

d. **Consequences** — You should be aware that information about a person's positive test results could cause problems with employment, insurance, etc. If they should confide in their coworkers, for instance, word could get out about their test results. The health department will guard confidentially by offering anonymous testing.

2. Decision to be tested

After reviewing these points, ask the patient, "Do you have any questions? If your results are positive, what will this mean to you? Are you still interested in taking this test after hearing all of this?"

3. Information about taking the test

If they decide to take the test, read or discuss the steps taken to preserve confidentiality. Stress the need to return the card to get their results. Patients should understand that the health department can do little more than offer them the test. They will be referred to their personal physician if results are positive.

4. General suggestions

If not previously discussed, explain what groups are at greater risk of contracting AIDS. It is particularly important that high risk group members follow the suggestions provided, whether or not they take the test. Even if results are negative, these suggestions should be followed because of the possibility of a false negative.

Protocol for Post-Test Counseling

No matter how much time was spent in pre-test counseling, test results must be carefully interpreted to the patient. Individuals in high-risk groups with negative results need to be properly counseled. The psychological impact of positive test results should not be underestimated. The patient is not necessarily prepared for positive results simply because he or she requested the test. Try to provide post-test counseling in a nonjudgmental manner. The counselor should be understanding and supportive. The following guidelines are suggested for post-test counseling.

Negative results

1. After informing patient of his negative results, discuss the possibility of a false negative. High-risk individuals could possibly be infected and able to spread the virus.
2. High-risk individuals with negative results need to be reminded not to donate blood and to continue safe sex practices (no exchange of body fluids/use a condom).

Positive results

1. Provide Information
   Review the points on the POST-TEST information sheet with the patient. Be ready to respond to any questions the patient may have.
   a. *This is NOT a test for AIDS.*
   b. *A positive test does NOT mean you have or will develop AIDS.*
   c. *Social relationships with family members may continue.*
   d. *Consult your physician/follow prevention precautions.*
      (1) Until properly evaluated, the individual should be considered infectious.
      (2) Discuss prevention — briefly review the list of precautions, respond to questions.

2. Referral
   a. Advise the patient to consult his/her personal physician for further medical evaluation. To

inform their physician, write "POSITIVE ELISA FOR HTLV-III ANTIBODIES" on the card with their code number. The patient should be requested to give this card to his/her physician.

b. If the patient does not have a personal physician or needs further information or would like referral to a support group, have them call the toll-free Hatline in Raleigh, 1-800-225-AIDS. This Hotline will be staffed from 8 am to 5 pm Monday through Friday beginning May 1, 1985.

c. If the patient is extremely emotional and you are concerned about their reaction to the information, consider contacting a community mental health center.

Pre-Test Information Sheet for the HTLV-III Antibody Test

If you want an HTLV-III antibody test, consider the following before making a decision:

1. This is NOT a test for AIDS. This test screens blood for antibodies to the virus (HTLV-III) thought to cause AIDS, thus helping to protect the nation's blood supply. Antibodies are what the body produces to fight infections.
2. A POSITIVE test does NOT mean a person has or will develop AIDS. Some tests will be falsely positive. For others, a positive test may mean one has been exposed to HTLV-III, and the virus may be present (this is especially true for high-risk group members). Based on what is known now, only a small number of people infected with the virus will develop AIDS.
3. A NEGATIVE test (especially for high risk groups members) does NOT mean an individual does not have or will not develop AIDS. It is possible to be infected with the virus and have a negative test.
4. Information about a person's positive test results could cause problems with insurance, employment, etc. Although health departments will offer anonymous testing, people should still be aware of these possible problems before taking this test.

Please consider this information carefully before you make the decision to have this test done.

For those who choose to have the test

Your name will not be used on any record or lab slip for this test. You will be given a card with a code number. To get your test results, bring this card to the health department seven days or later from the date you took the test. You will NOT be given your results unless you have your card. These steps are necessary to protect your privacy.

Positive test results

If your results are positive, you will be advised to seek medical evaluation from your personal physician. The health department is unable to provide this type of care.

High risk groups

Those in high risk groups are more likely to have been exposed to the virus causing AIDS. The following are thought to be high-risk:

1. Anyone with signs or symptoms of AIDS.
2. Males who have had sex with more than one male since 1979, and males whose sexual partner has had sex with more than one male since 1979.
3. Past or present abusers of injected drugs.
4. Hemophiliacs.
5. Sexual partners of persons in these groups.

General suggestions

Persons in high risk groups should NOT donate blood or blood products *regardless of their test results*. To reduce the chances of acquiring or spreading infection, limit the number of sex partners and use a condom.

Information for those with a Positive HTLV-III Antibody Test

1. This is *not* a test for AIDS!

If your test is positive, it means you may have been exposed to the virus and have developed antibodies (the body's defense against the virus).

2. A positive test does *not* mean that you have or will develop AIDS.

As with any other tests, there are people who are falsely positive. Some people may have a positive test who have never been exposed to the virus.

For others (especially high-risk group members), a positive test may mean one has been exposed to the virus. Even this does not mean you will develop AIDS. Based on what is known so far, only a small number of people infected with the virus will develop AIDS. In fact, many infected people may not develop any illness at all. There is no information at the present time to predict which persons with the antibodies are more likely to develop AIDS-related conditions or AIDS itself.

3. What does a positive test mean for family members?

There is no evidence to suggest that HTLV-III is spread by casual contact. Social relationships with family members and friends may continue.

4. Consult your physician for further evaluation.

If you have been exposed to the virus, you may be able to infect others. Until you have been checked by your physician, follow these steps:

a. Do not donate blood or plasma, sperm, body organs, or other tissues.

b. Avoid spreading the virus to

others through sexual intercourse and avoid exposure to saliva through oral-genital contact or intimate kissing. If you decide to continue sexual activities, use condoms.

c. Tell your sex partner(s) about your test result and encourage them to see a physician.

d. Avoid sharing personal items, such as razors and toothbrushes.

e. If you cut yourself and spill blood, wash the area where the blood has spilled with a water/bleach mixture (one part bleach to ten parts water).

f. Tell your physician and dentist about your positive test.

g. If you are a woman with a positive test, you should avoid pregnancy until you have been checked by your physician.

h. If you inject drugs, do not let others use needles you have used and do not use someone else's needles.

N.B. The information in this article is taken from instructions by the North Carolina Division of Health Services distributed to local health departments on establishing alternate test sites for HTLV-III antibody. It is provided for your information since it is entirely possible that you may have a patient referred to you with a positive test for this antibody. Because of limited funding and the fact that this test is available in commercial labs, the North Carolina Division of Health Services Lab will **not** be able to provide HTLV-III antibody testing for anyone except local health departments.

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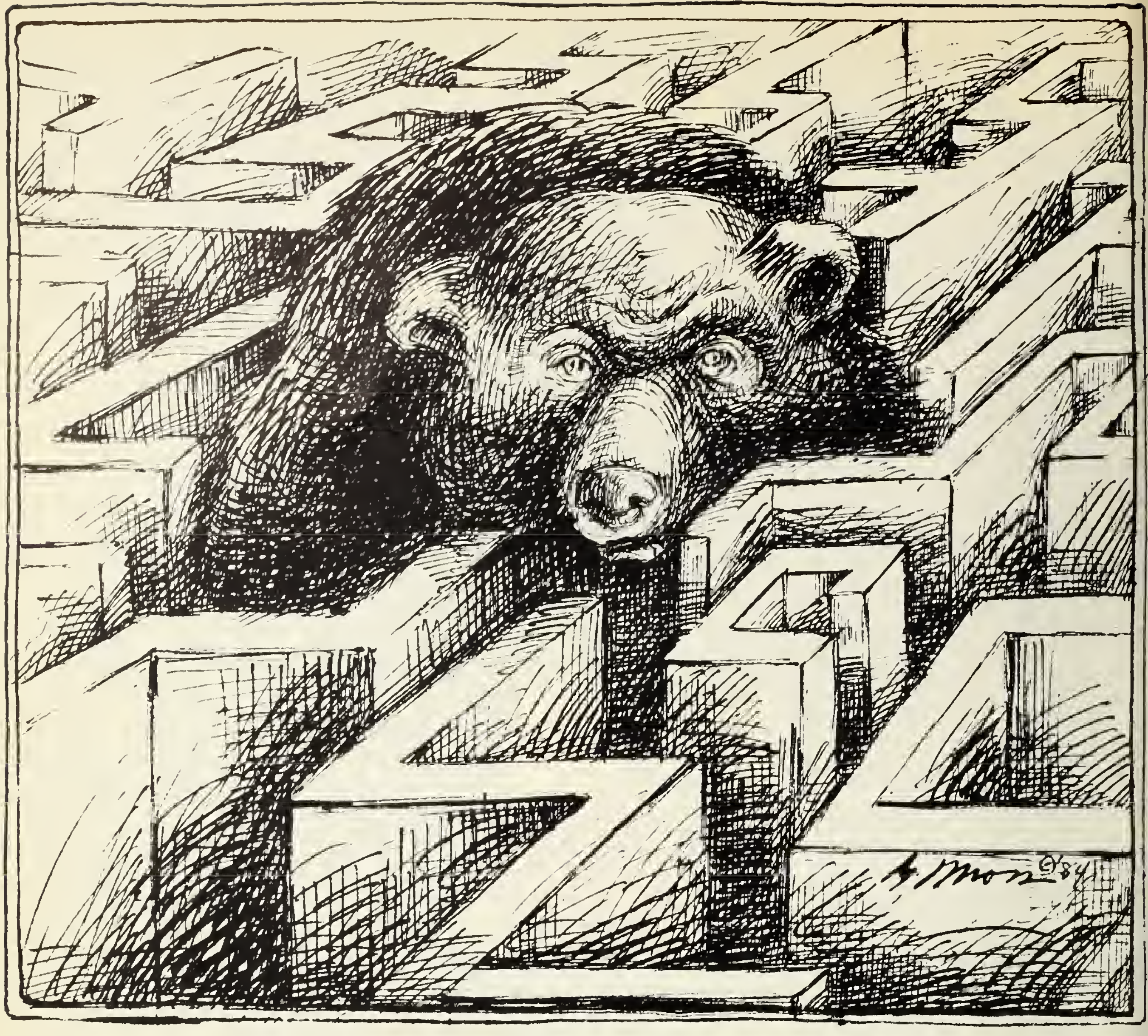

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See following page for brief summary of prescribing information.

SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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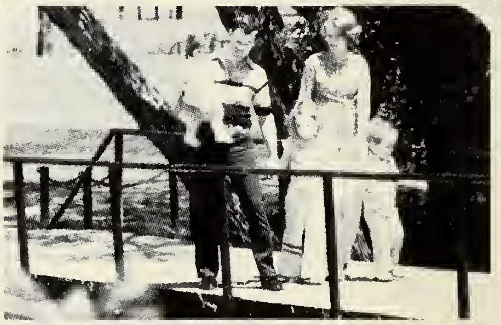

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Old Tobacco

John Henry McWhorter, M.D.

- *Tobacco has been a part of life in the Carolinas for a very long time.*

THROUGHOUT the millennia, man has repeatedly smoked various substances. Yet is is to the New World Indians that we owe the origin and smoking of tobacco.[1]

Originating from a word for a West Indian tube with which snuff was drawn into the nose, tobacco is a genus *(Nicotiana)* of the nightshade family *(Solanaceae)*. Only two of the more than fifty species have enjoyed historical importance — *N. tabacum,* indigenous to South America, and *N. rustica* of the West Indies and North America east and immediately west of the Mississippi River.[2]

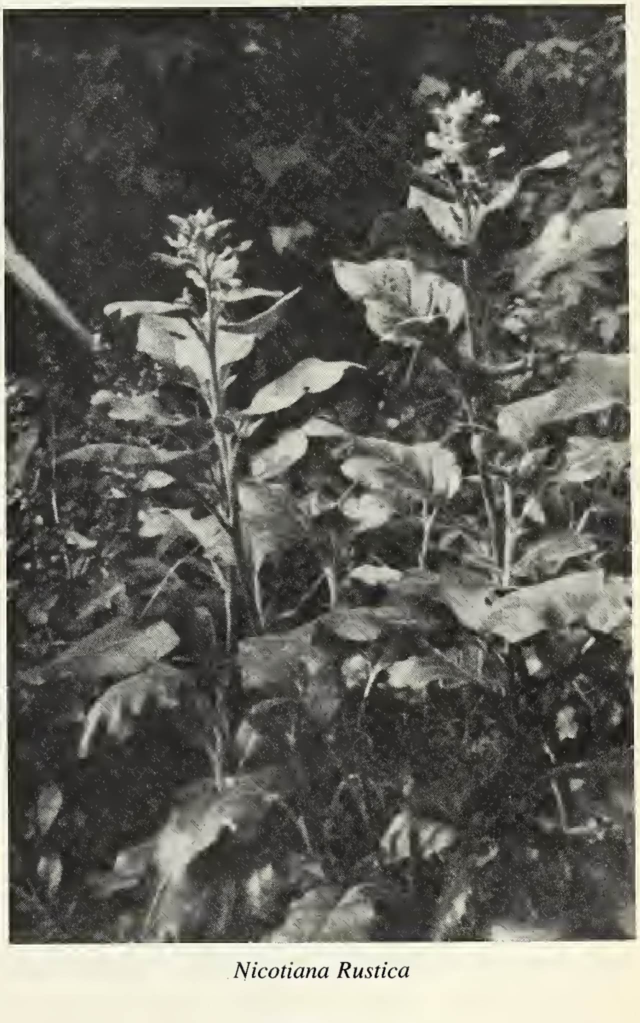
The colonists of 1586 returned from Virginia to England and planted *N. rustica* on their return.[2] The early European explorers seized upon tobacco as the panacea for their ills,[2] and addicted sailors spread the seeds to their ports of call.[3]

John Rolfe introduced the more aromatic *N. tabacum* in 1611 from the Spanish American plantations. The business success of the species soon established its dominance. A raging controversy over health hazards has raged since tobacco's introduction into European life.

The figure shows several plants of *N. rustica*. Its history among the native North Americans is an interesting one, not only from its patterns of use, but from its continued cultivation and use today, especially in the Carolinas. The myths surrounding its origin among the Cherokee offer a rich cultural lore. Its use was ritual and medicinal, rather than habitual. To the Cherokee, *N. rustica* was the original tobacco and was known to them as *tsâl-agăyûñ'li* or ‘‘old tobacco.’’ It was used as an incense or guarantor of an oath, and was smoked either communally or individually in a pipe, or sprinkled on a fire.[4]

The principal historical record of ‘‘old tobacco’’ among the Cherokee comes from the work of James Mooney and Frans Olbrechts, who translated Cherokee manuscripts, the most noted being that of Swimmer, a prominent medicine man of the time. They describe the use of dry, crushed *N. rustica* in a fire at a patient's house to keep witches away. Due to its scarcity, it was often mixed with ordinary smoking tobacco,[5] which is still done at present.

It was one of a few medicinal plants cultivated for use, as opposed to the custom of going up the mountains to collect them,[5] a practice still followed at the present time.



Nicotiana Rustica

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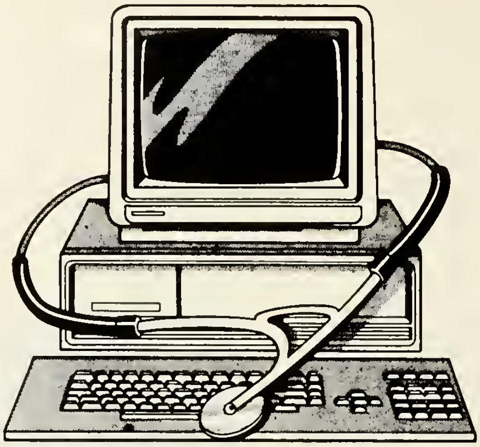

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Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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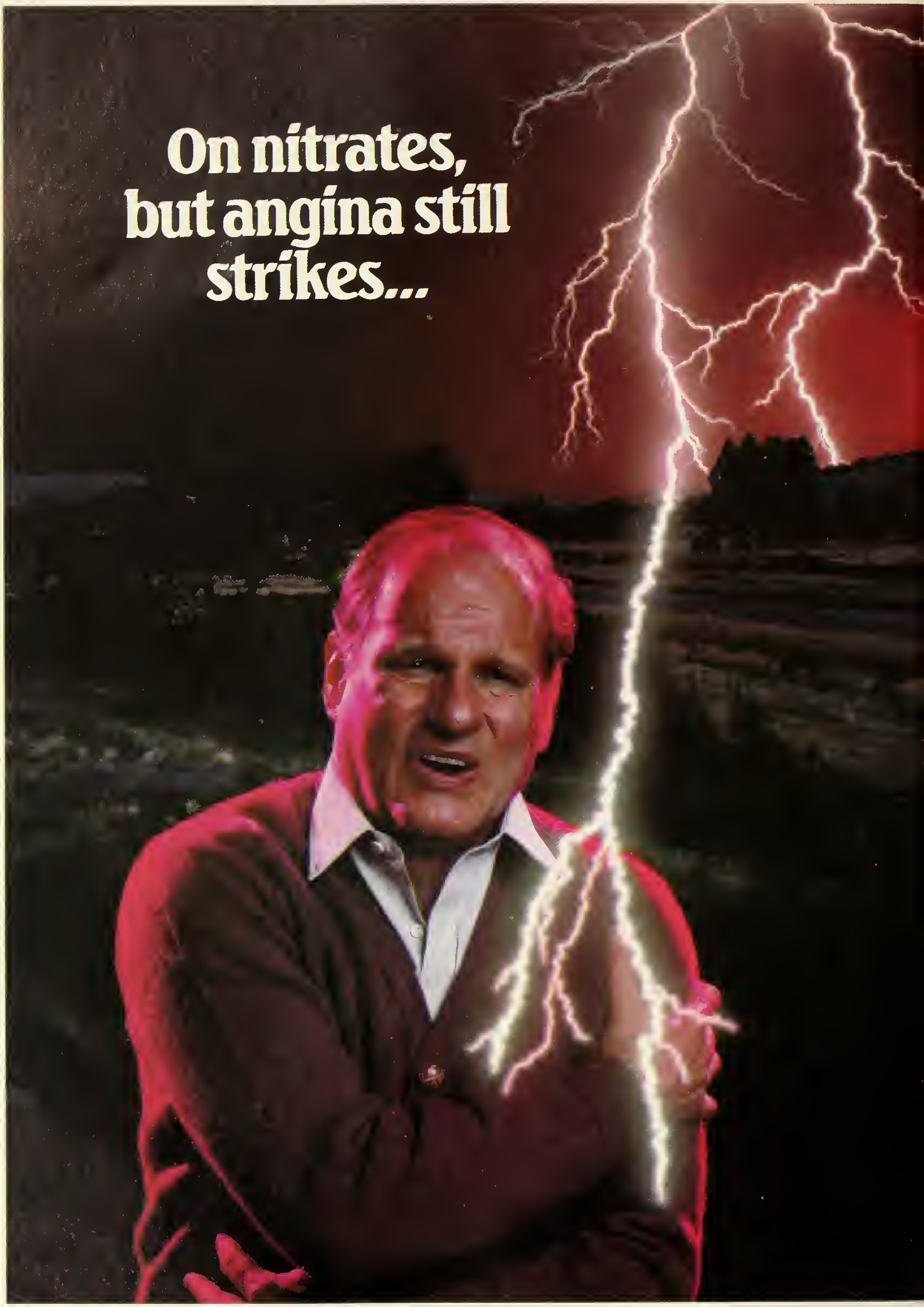
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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 2nd- or 3rd-degree AV block **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g , ejection fraction < 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker (See *Precautions.*) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before ISOPTIN is used. (Note interactions with digoxin under *Precautions.*) ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild and controlled by decrease in ISOPTIN dose). Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment, however, four cases of hepatocellular injury by verapamil have been proven by rechallenge. Periodic monitoring of liver function is prudent during verapamil therapy Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis) Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test *Pregnancy Category* C: There are no adequate and well-controlled studies in pregnant women This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2 9%), peripheral edema (1 7%), AV block 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3 6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported. (See *Warnings.*) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shakiness, claudication, hair loss, macules, spotty menstruation **How Supplied:** ISOPTIN (verapamil HCl) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984 2385

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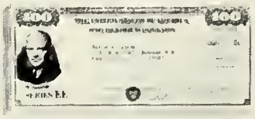

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CAROLINA HISTORY

Medical Student Research in the 1940s

John B. Graham, M.D.

- *This is Dr. Graham's address at the first convocation of the John B. Graham Research Society at UNC in January 1985.*

I was very impressed today by the quality of the research which you, our medical students, have been doing. I listened to 14 excellent papers. The contrast between these and what my contemporaries and I were doing at a similar stage of development is very stark. What I observed was the application of state-of-the-art concepts and procedures, and the positing of hypotheses which were gauged to obtain answers to serious questions. I thought it might be amusing for you to hear how different things were when I was a student 45 years ago.

I entered medical school in Chapel Hill from Davidson in the fall of 1938, completely unaware of the possibility that a medical student might be involved in research. Even if I had known, I probably would not have become so engaged. Like most of my peers, I was anxious to obtain my medical degree before we entered World War II, which was already getting underway in Europe. I would have regarded research as a potential diversion which might produce academic failure which would make me eligible for the draft, and the possibility of becoming a foot soldier. The irony is that the battalion surgeons of the US infantry in World War II, who were the most forward-placed of all doctors, were drawn largely from the medical school classes of 1941 and 1942 (my own). Despite my complete lack of clinical training and after having spent 2½ years in Pathology, I became the surgeon of the 2nd Battalion of the 307th Infantry, 77th Infantry Division and served in the battle of Okinawa.

The medical school in Chapel Hill consisted in 1938 of a two-year basic science curriculum, managed by about 20 bona fide faculty members for 60 students. Perhaps five of the faculty were doing publishable research. Research grants were unknown, except for a few Rockefeller and Markle Foundation grants, but the NIH as we know it today is a postwar phenomenon. One of the active researchers was the late Russell Holman of Pathology. He was helped in his experiments by a series of student research assistants of whom Dr. Margaret Swanton, formerly of our department and now practicing in Clinton, was one. Another was Dr. Gilmer Mebane who still practices in Rutherfordton. Arnold Breckenridge, who lost his life in service during World War II and is memorialized by the Spicer-Breckenridge Lectureship, performed a similar function for Dr. MacNider. These students were working their way through a two-year curriculum over a three-year period as research assistants. My guess is that they received little compensation other than remission of tuition.

At Cornell, where I did my clinical years, a few of my classmates also did research as students. Three of them — Charles Breedis, Carleton Hunt, and Walter Riker — went on to become prominent scientists, but most of my contemporaries at Cornell were driven by the same imperatives as those at Chapel Hill and were headed for war and practice. I had very little contact with the faculty at Cornell until my final semester which began immediately after Pearl Harbor. Two of the three Pathology residents were being drafted, and I was asked to start my internship six months early to help fill the manpower gap. This meant that I would be given room, board, uniforms and laundry in exchange for doing autopsies at night and on the weekends. I was also expected to operate the Blood Bank on alternate nights. The "take home pay" was $25 a month, provided by the Blood Bank. My mother and I welcomed this financial assistance, but I essentially dropped out of medical school. I never attended clinics in the surgical specialties, and to this day I am completely ignorant of Ophthalmology, Urology, ENT, and Orthopedics (I hope it doesn't show!). I spent 2½ years as a house officer in Pathology at the New York Hospital, however, and it was during this period that my research career began. I can only characterize these activities as "what happens when you are just standing around." I think you will see what I mean.

My first publication[1] grew out of an autopsy and concerns a disease of the kidney which was then so obscure that there was not a description of it in the English language. My involvement came about this way. (Ruby, my then recently-acquired wife, remembers it well.)

Pathology residents at New York Hospital in those days did all the autopsies performed at night and on weekends. The senior staff did the daytime cases, Monday-Friday. This policy was based on the premise that an autopsy was an important teaching exercise and that the most, not the least, experienced persons should do them if possible. (WW II changed many things in addition to the face of Europe. I doubt that many living physicians have ever seen a Professor do an autopsy.) The time was the fall of 1943, I think, when I was for a short period the only house officer in Pathology. At about 8 o'clock on a Sunday morning, the telephone rang. "Autopsy, Dr. Graham, and the clinician wants it done right away." I griped and my wife grumbled, but I got dressed and went to the morgue. The deceased was a small girl. Her main clinical problem appeared to have been severe anemia which had required transfusions, but she had also been uremic. I found her kidneys to be small

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From the Department of Pathology, UNC, Chapel Hill 27514.

and fibrotic and to contain many small cysts. These were unusual in being located in the medullary regions rather than the cortices. I completed the autopsy as rapidly as I could and returned home to read the *New York Times*.

It later transpired that a similar case had been observed in Germany in the 1920s, but this single report was essentially unknown except to the readers of Henke-Lubarsch's *Encyclopedia of Pathology*, an 18 volume set printed in German. Fortunately, we had access to Henke-Lubarsch, because Dr. William Dock, the Professor, was fluent in German. He uncovered the previous case for us. We designated the syndrome "Medullary Cysts of the Kidney with Anemia," anemia being included in the title because the clinician was Dr. Carl Smith, the hospital's pediatric hematologist, the person to whom the child had been referred.

I consulted Carl Gottschalk's two-volume text on kidney disease yesterday (it is mysteriously entitled *Strauss and Welt's Diseases of the Kidney*, 3rd edition) to see whether he had gotten the story straight. I was pleased at how his account begins: "In 1945, Smith and Graham reported the case of an eight year old white girl who presented with severe anemia of 1 year's duration, who was suffering from renal failure, and whose kidneys at death were found to have medullary but not cortical cysts. In the 3 decades since then over 250 cases . . . have appeared in the literature, etc." The point of this story is that I became an author solely because a child had died on the weekend when no one else was available to do the autopsy. If she had survived until Monday, one of the senior staff would have done the case and become the co-author. This event emphasizes the importance of careful scientific planning.

My next publication is one which I have never discussed publicly. In fact, I did not list it in my CV for 25 years fearing that, if my association with it were known, it might jeopardize my career. Now that I am retiring, I shall come out of the closet, and tell all.

When I left New York Hospital in July 1944, I joined the Army and spent 18 months overseas in the Pacific Islands and Japan. I returned to Chapel Hill in September 1946, and sometime during the next year received a letter requesting a reprint of a paper in the *Journal of Investigative Dermatology*. I thought there must be some mistake and visited the library. I discovered to my astonishment that I was an unbeknownst author. The title of the paper which I had co-authored was "Absence of Thrombo-angiitis Obliterans in Experimental Dermatophytosis."[2] The text explained that the authors had produced chronic infections of the footpads of 8 castrated (?) rabbits, had maintained the infections for 18 months, and had then demonstrated that obliterative arterial lesions were not present in their lower extremities. The patency of the arteries had been demonstrated by injecting them through the aorta with radio-opaque material and X-raying the legs. (This is the same procedure which Dr. Fred Dalldorf still uses at NC Memorial to examine the coronary arteries in patients who have died of heart disease.)

Suddenly the penny dropped. I remembered what had happened. I had been having lunch in the doctors' dining room at the New York Hospital with an affable dermatologist who had been repatriated from Shanghai on the Gripsholm several years earlier. He was trying to figure out how to examine the arteries of some rabbits which might have developed obliterative arteritis in their lower legs. I casually suggested that he might inject the arteries with a radio-opaque mass and X-ray the legs. The next morning when I came to work, I found a dead rabbit in front of my office door wrapped in a newspaper. I took the rabbit to the morgue out of curiosity, injected the aorta, X-rayed the legs, and obtained a nice arterial pattern. The following day I found another dead rabbit in front of my door. This pattern was repeated for, I suppose, a week since the paper mentioned eight rabbits. But I was very busy at the time and really didn't want to become involved with such a "mickey-mouse" project. I was now the Resident and had only one helper, a dumb intern from California named Sam. He and I were having to do *all* the autopsies, because the draft had finally caught up with the faculty. I tried to get Sam interested in the research project, but he wasn't as dumb as I had thought. So I placed the dead rabbits out of sight in a refrigerator to wait until I could get to them. My last act at the New York Hospital before departing for Carlisle Barracks in July was to inject the refrigerated rabbits, X-ray their legs, and send the films to the dermatologist. I had completely repressed the memory of those silly rabbits, and had I not received a reprint request, I should never have known that I am an authority on the non-relationship between athlete's foot and Buerger's disease. I don't know what the moral of the story is, except it certainly was easy to become a research collaborator in the old days!

My final story concerns Dr. Saxton's rats. He was studying cancer in rats using Harry Green's technique of implanting a bit of tissue in the anterior chamber of the eye and observing it directly. The rule-of-thumb was that benign tissue regresses and malignant tissue extends. He was interested in chromophobe adenomas of the rat pituitary, and had transplanted small bits into the eyes of about 50 rats. (The next step in his protocol was to sit back to see what happened, and the experimental period was up to two years of observation!)

In the middle of his experiment Dr. Saxton got an offer to move to Washington University in St. Louis, his home town. He asked me to continue measuring the size of the tumors at monthly intervals, then remove the tissue for sectioning at the end of the experiment. I followed his instructions, more or less, and he was kind enough to place my name on his paper.[3] Just before leaving New York, I received a letter from a well known cancer researcher asking a technical question about the experiment. He wished to know why we had anesthesized our rats with chloroform rather than ether when implanting the tumors. I didn't have a clue. In fact I had never seen Dr. Saxton operate. I called him in St. Louis and, after reprimanding me for making an unnecessary call during wartime, he explained. "It is very obvious. I like to smoke when I operate, and chloroform is not explosive like ether."

I think I learned an important lesson from Dr. Saxton's rats. I have been very skeptical ever since about the significance of the very detailed descriptions of "Methods and Materials" which one finds in certain journals (e.g., *JBC*, *JCI*). I have found it to be faster, cheaper and more rewarding to visit the lab of someone who has developed a new technique than to try to establish the procedure from what has been printed. Very often something crucial has been omitted and the omission not recognized because of the verbiage. These tedious descriptions are more valuable sociologically than scientifically.

But the phrase ''smoking while operating'' has a very contemporary ring. It reminds me of a recent story in my favorite newspaper. You may recall that at the Baby Doc School of Medicine in Port-au-Prince, Haiti while Dr. Janata was transplanting the liberal heart of a Volvo-driving Yuppie into the conservative body of a banker, President Raoul Duke stood by the operating table unmasked, with a can of beer in his hand and a cigarette holder in his mouth. Could it be that Raoul Duke is one of Dr. Saxton's descendents?

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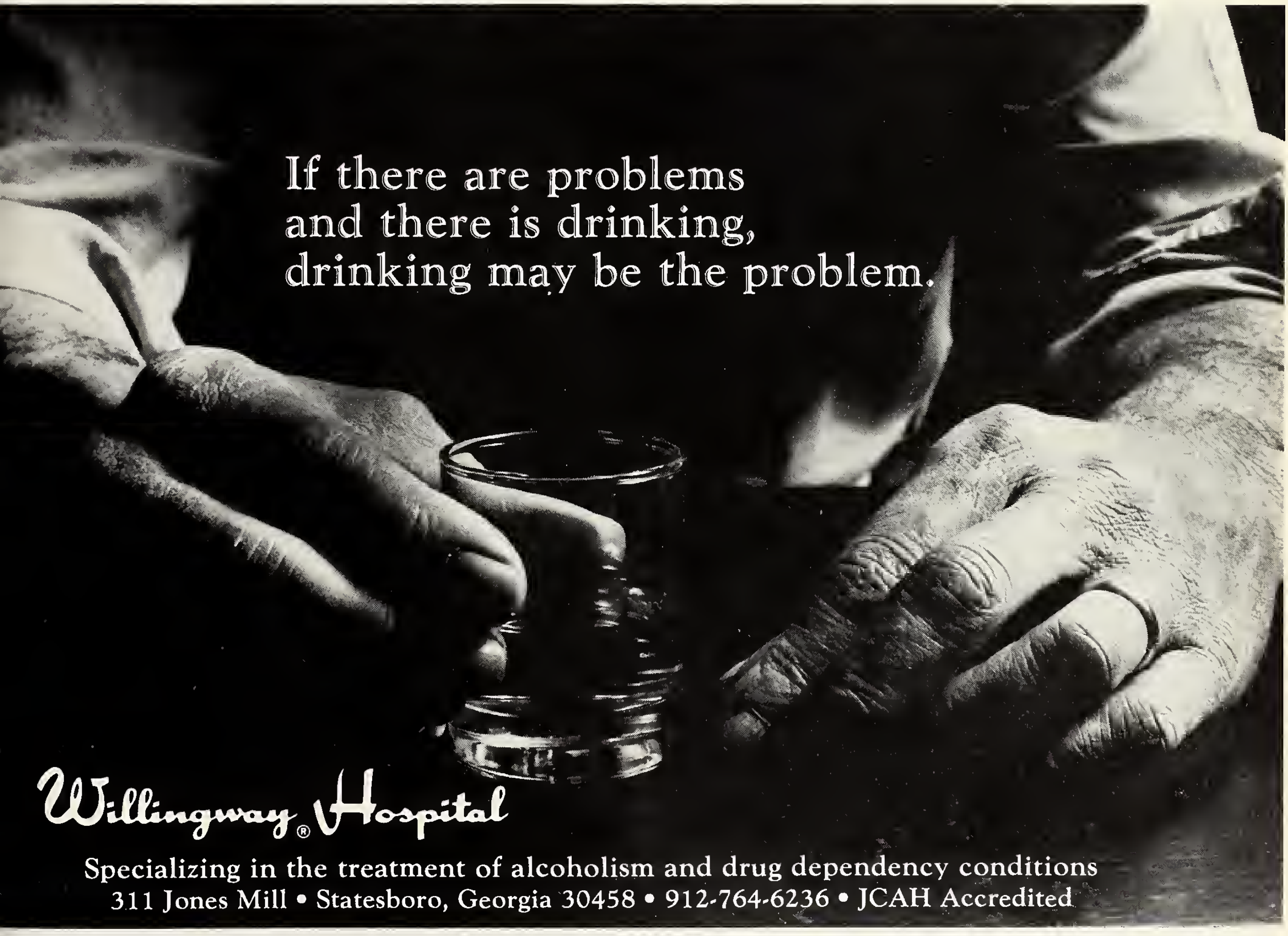

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NORTH CAROLINA MEDICINE TODAY

Aging in its many aspects

It is estimated that 25 million people (11% of the population) are over age 65, and represent the fastest-growing segment of the population by far. It is further estimated that this group currently spends approximately 75 billion dollars annually for personal health care, and accounts for some 55% of all federal health dollars.[1] For these reasons alone, studies concerned with various aspects of aging are of vital importance to the entire nation. Much major research in this complex area is being conducted in North Carolina, at its several medical centers and universities, often under grants from the National Institute on Aging.

Studies cover a wide range

Recent studies have reported on the physiological dynamics of aging as related to circulatory diseases and circulatory risk factors at advanced ages (over 85) as compared to findings in a study population with a mean age of over 70 years.[2] Another study, stemming from the comprehensive Duke First Longitudinal Study, evaluated Wechsler Memory Scale scores as related to distance from death and the potential use of the WMS as a predictor of survival in both normal and demented elderly populations,[3] while yet another compared young and old adults in the spontaneous use of context to learn and recall information.[4]

Dealing with America's fourth leading killer disease

Researchers at Duke University Center for the Study of Aging are focusing on the study of Alzheimer's disease, a type of primary neuronal degeneration that is the most common form of dementia. Estimates vary but indicate that as many as 4 million older Americans[1] are afflicted with this illness, which has been labeled "the disease of the century."[5] Concurrent with its medical research on Alzheimer's disease, the Duke University Center is providing innovative support mechanisms for afflicted families and other caretakers. A hotline provides callers with telephone consultations, introductions to others close by in similar circumstances, and practical medical, legal and psychological information. The Center has also aided in the establishment of 19 local support groups statewide, and regularly makes available information on Alzheimer's disease to health providers, nursing homes and hospitals, and others responsible for programs and services directed toward the victims of this killer disease.[6]

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*Feighner JP, *et al: Psychopharmacology* 61:217-225, Mar 22, 1979.

Please see summary of product information on following page.

LIMBITROL® Ⓒ Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

> ***Usage in Pregnancy:*** **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: *Double strength (DS) Tablets,* white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets,* blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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EDITORIAL

In Support of a Model Bill Allowing the Use of Insect Sting Kits by Trained Laymen

Claude A. Frazier, M.D.

I have good news and bad news. The bad news is that any one of you could be stung and die within five minutes; you would not have to have had a previous reaction to an insect sting. The good news is that someone might be present who had a pre-packaged epinephrine syringe and was trained to give an injection. He could buy time to get you to a physician or hospital.

Some years ago, after treating a number of patients who suffered near fatal anaphylactic shock reactions to insect venom, I determined to make this branch of allergy a focus of my concern, and I gathered as much information as I could on the subject. This appeared in 1969 as a textbook, *Insect Allergy — Allergic and Toxic Reactions to Insects and Other Arthropods,* published by Warren H. Green, Inc. in St. Louis. A revised edition will be published soon.

Over the years I have discovered a good deal of ignorance not only among the general public but also among physicians as to both symptoms and proper treatment of an anaphylactic reaction to an insect sting. A number of fatal reactions have been misdiagnosed as "heart attack" or "death from natural causes," so the problem is greater than statistics presently indicate. I believe most of these deaths were unnecessary.

Anaphylactic shock reactions to food or drugs are perhaps more likely to be correctly diagnosed simply because no other cause seems reasonable at the moment. Someone who has just eaten shellfish, for instance, and then almost immediately exhibits systemic symptoms is more likely to recognize the cause as "something he ate." Allergy to insect venom is often surrounded by misunderstanding and misinformation.

After suffering an anaphylactic shock reaction to an insect sting, some patients have been told by their physicians to simply take benadryl the next time they are stung. In my hometown, a physician gave benadryl to a young man who had a history of reaction to an insect sting. This man was in the woods fishing, in an isolated area, and was stung. He died. His mother, having been told by one of my patients about the insect sting kit, called me three different times to ask if her son's death could have been prevented. To keep the doctor from being sued and to relieve her guilt, I told her that nothing was 100%. That same doctor was seated next to me at a medical meeting later and he had seen another patient similar to the one who had died. "What did you give him to carry?" I asked. His answer, "Benadryl."

Benadryl will not stave off a severe systemic reaction. On the other hand, only a small dose (0.3 to 0.5 cc) of injectable epinephrine can give pause to rapidly intensifying and potentially fatal anaphylaxis long enough to transport the patient to a physician or hospital.

I can cite a number of cases of both fatal reactions and misdiagnoses. For example, an obituary in a local paper states that a 57-year-old man was stung in the arm while fixing his car; he was dead on arrival at a hospital less than an hour later. No one, evidently, was aware that he was allergic to bee venom.

For example, a well-known newspaper man was out jogging and his death was attributed to acute heart failure. Even though just before he collapsed he was heard to say that he had been stung and the autopsy findings were consistent with fatal anaphylactic shock, his death was misdiagnosed.

A man died unexpectedly while on a fishing trip in Transylvania County. He had suffered a bee sting before death occurred.

A pediatrician called me to say that three of his young patients were allergic to insect stings but that the school nurses could not give them a dosage of epinephrine if they were to be stung. He said, "Would you call this stupid Superintendent of Education and tell him to make them treat these patients if they are stung?" I explained to him that it was not a stupid superintendent but a stupid State law. I suggested the "Good Samaritan law" but he said, "These school nurses and teachers will not do anything until it is a written law of this State. They are afraid."

Fatal outcomes can be prevented. Death due to venom from one or two insects, from the ingestion of a food or the injection of a drug is essentially needless. Programs to train people who are in positions of responsibility for public safety to recognize systemic symptoms of allergy and to administer pre-measured injectable epinephrine subcutaneously when a physician is unavailable can save lives that might otherwise be lost.

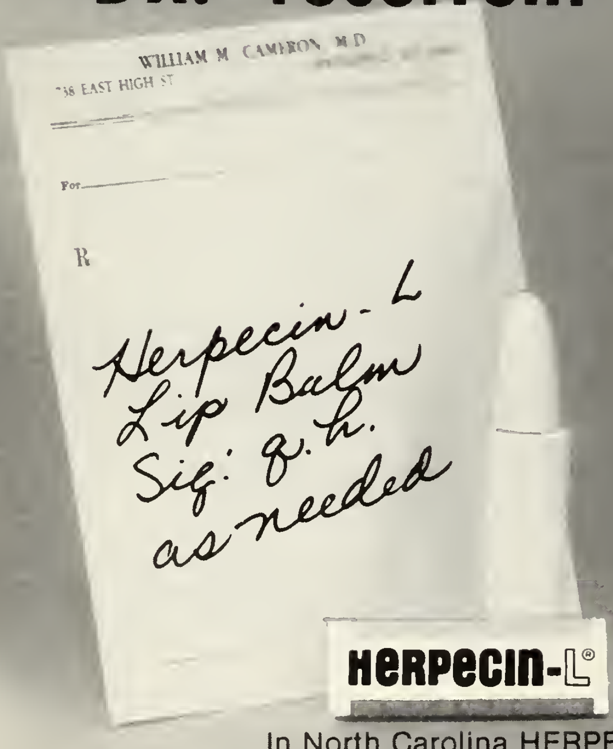
Such a program has received the support of the American College of Allergists, the American Academy of Allergy, the American Academy of Pediatrics and the American Academy of Family Practice. It has also been commended by a number of physicians as a step toward emergency first-aid care for the public.

From Bldg. 4, Doctors Park, Asheville 28801.

The most recent development has been for the American Medical Association to revise the previous version of the model bill. I have worked with the legislative branch of the AMA for years trying to work out a model bill. At one point I thought they might withhold their support by rescinding the model bill. At that point I had to speak before the legislative branch and try to convince them otherwise. Since that time support has been stronger than ever. The revised edition of the model bill will discourage lawsuits being brought against the trained layman who administers epinephrine as a "good samaritan."

Only in the 10 states that have passed laws allowing trained laymen to administer the pre-measured epinephrine can a layman legally give this treatment to a person who is suffering an anaphylactic shock. Georgia may become number 11. North Carolina passed its bill on June 11, 1981.

Dx: recurrent herpes labialis



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Brief Summary of Prescribing Information
NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information A Brief Summary follows

DESCRIPTION

Norlestrin Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE

Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0 05 per 100 woman-years, in clinical trials with Norlestrin 2 5/50 involving 96,388 cycles, there was a pregnancy rate of 0 22 per 100 woman-years

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance

CONTRAINDICATIONS

1 Thrombophlebitis or thromboembolic disorders
2 A past history of deep-vein thrombophlebitis or thromboembolic disorders
3 Cerebral vascular or coronary artery disease
4 Known or suspected carcinoma of the breast
5 Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding
7 Known or suspected pregnancy (See WARNING No 5)
8 Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1 *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2 0 times greater in users than nonusers, and the risk of thrombotic stroke was 4 0 to 9 5 times greater

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not Oral contraceptives, however, were found to be a clear additional risk factor

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke The amount of smoking is also an important factor

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth with the exception of oral contraceptives in women over 40 who smoke

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders Should any occur or be suspected, the drug should be discontinued immediately

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization

2 *Ocular Lesions* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions

3 *Carcinoma* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives Close clinical surveillance of users is, nevertheless, essential In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding appropriate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care

4 *Hepatic Tumors* Benign hepatic adenomas have been found to be associated with oral contraceptives Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives The relationship of these drugs to this type of malignancy is not known at this time

5 *Usage in or Immediately Preceding Pregnancy, Birth Defects in Offspring and Malignancy in Female Offspring* During early pregnancy female sex hormones may seriously damage the offspring

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptives should be withheld until pregnancy has been ruled out If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy

6 *Gallbladder Disease* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives

7 *Carbohydrate and Lipid Metabolic Effects* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed

8 *Elevated Blood Pressure* An increase in blood pressure has been reported in patients receiving oral contraceptives The prevalence in users increases with longer exposure Age is also strongly correlated with development of hypertension Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure

9 *Headache* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives

10 *Bleeding Irregularities* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives In breakthrough bleeding nonfunctional causes should be borne in mind In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives

11 *Ectopic Pregnancy* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures

12 *Breast-Feeding* Oral contraceptives may interfere with lactation Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs

PRECAUTIONS

1 A complete medical and family history should be taken prior to the initiation of oral contraceptives The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination

2 Preexisting uterine leiomyomata may increase in size

3 Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree

4 Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated

5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice If jaundice develops, the medication should be discontinued

6 Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function

7 Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency

8 Serum folate levels may be depressed

9 The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted

10 Certain endocrine and liver function tests and blood components may be affected

(a) Increased sulfobromophthalein retention (b) Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone (d) Decreased pregnanediol excretion (e) Reduced response to metyrapone test

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates phenylbutazone phenytoin sodium, tetracycline and ampicillin.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives thrombophlebitis pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease benign hepatomas, congenital anomalies

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related nausea and/or vomiting, usually the most common adverse reactions occur in approximately 10% or less of patients during the first cycle Other reactions as a general rule, are seen much less frequently or only occasionally gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow dysmenorrhea amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma, breast changes, change in weight, change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature intolerance to contact lenses

The following adverse reactions have been reported and the association has been neither confirmed nor refuted premenstrual-like syndrome, cataracts, changes in libido, chorea changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication

After several months on treatment, bleeding may be reduced to a point of virtual absence, reduced flow may be a result of medication and not indicative of pregnancy

HOW SUPPLIED

Norlestrin $\boxed{21}$ 1/50 is available in compacts each containing 21 tablets Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{21}$ 2 5/50 is available in compacts each containing 21 tablets Each tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{Fe}$ 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

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Ecology and Pollution

Eugene W. Linfors, M.D., editor

The question for June is: **What would you advise the North Carolina Medical Society to do and say publicly about ecology and pollution?**

From Dr. Robert M. Hall, Director of Wake County's Department of Health.

What the North Carolina Medical Society, as well as its individual members, can do and say publicly on ecology and pollution was stated very clearly by the participants in an Environmental Health Seminar held in October, 1984 at which the Society was represented. As reported to the Society's President it was the unanimous opinion of the participants that,

> The greatest and most immediate environmental threat that now faces us all is the pollution of our water supplies. Our greatest and most urgent environmental need is for individuals and organizations who are interested in the public's health to become involved in land use planning and land development in suburban and rural areas in order to prevent this pollution of our water.

Urgent as this environmental need was said to be, it is made even more so by the moves now underway in North Carolina to eliminate local boards of health and even to eliminate local health departments and disperse their functions among other elements of county government.

The Environmental Health Seminar was held in Atlanta and was sponsored by the American Medical Association. Its purpose was to focus attention on major environmental and occupational health problems and to encourage cooperative efforts to respond to these problems within the eight southeastern states.

The participants included representatives from the various state medical societies, occupational medical associations, health departments, environmental protection agencies and schools of public health in the eight states, and the United States Centers for Disease Control and the United States Environmental Protection Agency.

The seminar participants were requested to identify the environmental and occupational health problems and needs that confront the populations of these states and recommend appropriate solutions. This they did, identifying specific problems that we face now, as well as others that are potential in nature. As stated earlier, they agreed that the greatest current, specific environmental problem is the threat of pollution of our water supplies as the result of unplanned and uncontrolled land development.

The participants also identified problems or needs of a general nature that must be satisfied if the specific environmental health problems are to be solved.

Communications. The lack of and the resulting need for adequate communications between agencies, organizations and individuals with similar interests, goals and responsibilities in the fields of environmental and occupational health was stressed more often than was any other problem. It was a theme that ran throughout the seminar.

This lack of the necessary communications exists not only between the states, and between them and federal agencies, but within the states themselves. Within the states there are gaps in communications between the various state agencies, between public and private agencies and organizations, and between them and individual, practicing physicians and organized medical entities.

Coordination of Efforts. The lack of and the need for the coordination of the efforts of the various organizations, agencies and individuals with similar interests, goals and responsibilities in the fields of environmental and occupational health was mentioned next most often, as was the obvious fact that the coordination of efforts is dependent upon the necessary communications.

Influence of the Practicing Physician and of Organized Medicine. The importance of and the key role played by the individual, practicing physician and by medical societies was emphasized repeatedly. This was not done by the physicians present, who were in the minority, but by the non-physician participants. At least some of the physicians present were surprised at the importance and influence attributed to them and their efforts by the other participants and found this a somewhat sobering experience.

The participants stressed that both the individual, practicing physician and organized medicine play a key role with respect to the identification of environmental and occupational health problems, the advocacy of the measures that are necessary for their solution and the necessary education of patients, the community and elected representatives.

Education. Physicians are the best possible educators with respect to environmental and occupational health problems and hazards. The need for the education of patients, community groups and legislators was stressed, as was the need for objectivity. Facts must be used; if opinions are stated, they should be identified as such.

Advocacy. Physicians can marshall support and lobby for the definition of public health problems and the measures required for their solution. The Mississippi State Medical Association has opposed, officially and actively, all attempts to establish a high level nuclear waste repository in Mississippi prior to the availability of data assuring the safety of such a program. At the Seminar its representative urged the "Medical Associations of our sister states to carefully examine the hazards associated with the transportation of high level nuclear wastes through their cities and for the American Medical Association to take a more active leadership role in advising our fellow physicians and the public at large of the health risks of nuclear wastes."

Protagonists on Behalf of the Public's Health. The governmental agencies are unable to lobby on behalf of environmental and occupational health programs. It is essential that non-governmental organizations, such as medical societies, carry out the necessary educational and lobbying measures.

In addition to identifying current and potential environmental health problems and needs, the participants also identified barriers to the prevention of pollution, such as cost, lack of sufficient information, etc. They agreed that the biggest barrier, however, is "politics" and the influence that sometimes is exerted by industry.

This stated need for the protection of our water supplies lends even greater urgency to the need to retain the local boards of health and health departments which protect our people from pollution of their water supplies, as well as from other environmental hazards.

The physicians of the state should know that now, when North Carolina's people face greater environmental health problems than ever before, a move is underway in the state that will eliminate local boards of health and have their functions and responsibilities taken over by county commissioners. Another move is underway that would allow the elimination of local health departments and the assignment of their functions to other agencies of county government. Among those functions are those of the sanitarians who protect not only our water supplies but our milk and other foods and who carry out our epidemiological investigations.

Still other moves have been designed to eliminate the qualified health department directors who supervise and direct these environmental protection activities, among others.

Wake County, as has others, has attempted to prevent the hiring of qualified physicians with public health training and experience as health directors and has attempted to replace these with lay "administrators."

Since public health problems would not even be thought of, much less planned and prepared for, if qualified professionals are not available, one can only surmise why this would be done. One possible reason may be represented by the complete support that has been given the Wake County Board of Health and Health Department by the Wake County Medical Society and its Public Health Committee as the result of the interrelationship between the Committee, the Society and the physician health director.

Another reason may be represented by this article and the influence of those to whom it is addressed.

These moves are made possible by a North Carolina law, N.C.G.S. 153A-77, which authorizes the board of county commissioners in a county that has a population in excess of 325,000 to assume direct control of the activities performed by the county boards of health, mental health, social services and any other boards appointed by them.

Left unanswered is the question of why such a county, with greater and more complex problems as the result of an increasing population would not need these various boards more than ever. An even more pressing question is why this would be done when it is manifestly impossible for the county commissioners to carry out the additional responsibilities of these various boards.

Only one county, Mecklenburg, had a population of this size when the law was passed, in 1974. The Mecklenburg County Board of Health was then eliminated, after which the county commissioners assumed its functions. The health department was then fragmented and a separate department of environmental health was established. The county now has eliminated the boards of mental health and social services and is in the process of placing the remainder of the county health department under an assistant county manager.

Wake and other counties have attempted to do the same thing by having the law amended so that it would apply to counties with populations of less than 325,000.

The current law, while it allows the elimination of the board of health, prevents the elimination of the health department.

Legislation now being proposed for submission in the current session of the North Carolina General Assembly would make this possible.* If it is enacted the commissioners of a county will be able, after abolishing the board of health, to abolish the health department and transfer its functions, including those that protect against pollution of the environment and in effect regulate development, to other departments of the county government.

These proposals and actions have been made in the name of "efficiency," "economy," "the streamlining of county government" and "making county government more responsive to the people."

Other proposals have been made that would consolidate the county health department, after elimination of the board of health and the health director, in a Department of Human Services. "Public Health" as an entity would disappear as its personnel and activities would be grouped, together with those of "other welfare agencies" and the whole placed under a politically appointed lay administrator.

These are reasons why the North Carolina Medical Society has come to the defense of the state's local boards of health. These are the key elements in the system of environmental protection and other public health measures that the Society itself pioneered in 1877. Now, over a century later the Society again has initiated actions designed primarily to prevent the pollution of water supplies, but also to protect against other environmental hazards.

At the suggestion of the Wake County Medical Society, which had taken the same step previously, the Society adopted a resolution supporting the repeal of N.C.G.S. 153A-77. Stating that " . . . organized medicine spawned public health in the State of North Carolina and has nurtured it throughout its history," the resolution continued by stating that "duly constituted statutory boards of health provide a reasoned, professional, informed buffer between the political pressures upon city councils and county commissions and the needs driven pressures upon the local public health agency'' and concluded by supporting repeal of this law that makes possible the elimination of boards of health. It then approved the transmittal of the Society's action to other professional societies and organizations along with encouragement for them to support repeal of this law, also.

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* House Bill 604 submitted to the General Assembly from Mecklenburg County.

Other professional organizations have taken similar actions at the county and at the state level.

The processes of communications and of coordination of efforts that were declared to be vital by the participants at the seminar in Atlanta have begun. They must continue and be expanded so that there will be the necessary coordination of efforts with other agencies, organizations and individuals with similar interests and goals, at the county and at the state levels.

It remains now for the physicians of the state, individually and as organization entities, to play the key role outlined for them at the Environmental Health Seminar in Atlanta. It is they who must educate and advocate.

This is necessary if our state is going to retain its local boards of health, health departments and qualified public health professionals, and if our health department personnel are going to be insulated from political, economic and developmental pressures as they work to protect our communities from water-borne and other environmental hazards.

We need to act as if our lives depend on it. They just might. So might those of our children and of their children, also.

From Dr. Axalla J. Hoole, an internist in Chapel Hill.

One can easily be misunderstood in making suggestions about ecology and the environment to a group (a county medical society) that might consider these issues tangential; for the term ecology brings out social and political emotions rather than medical ones. An activist for ecological issues is more likely to be thought a crazed member of a different political party or a socialist with anti-capitalist leanings than a physician who considers problems of the environment and ecology genuinely important to health and topics that should be considered by county health societies. I personally take the latter view, and feel that many of the medical problems we face in the future will be created by man's misuse of his environment. Physicians will be asked for opinions and solutions.

If I were to make a suggestion to a county medical society, I would use PSR (Physicians for Social Responsibility) as my model. This is a non-partisan group that has taken the position that nuclear war presents the greatest long-range threat to the health of mankind; though education PSR hopes to practice preventive medicine. Presentations by this group have been very important in debunking the myth that organized medicine can somehow ameliorate the results of a nuclear disaster; through presentations of many kinds they have helped people understand the medical consequences of nuclear war. I would suggest to a county medical society that in a similar way a few programs be set aside each year for presentations of environmental issues (acid rain, food additives, nuclear waste disposal — our potential for hurting ourselves is seemingly limitless) so that members of the society might consider the seriousness of the problem and consider appropriate responses as a group or as individuals.

It is clear that the famine in Africa has been brought about in part by ecological abuses — overpopulation, overgrazing of pastures, changes in agricultural practices; the response of organized medical care in a traditional sense is now almost irrelevant. When would it have been appropriate for physicians to accept the consequences of these abuses as health problems, and through education and understanding sought to intervene?

From Dr. Morris A. Lipton, a psychiatrist in Chapel Hill.

In the 200 years since the Industrial Revolution, man has changed the earth more than all other species since the beginning of life several billion years ago. Man's population quadrupled and continues to grow rapidly. Man's immediate needs for food, energy and manufactured goods and the profits derived from generating and distributing them are so great that we tend to ignore their longer range consequences. Thus, we tolerate the depletion of natural resources such as forests and soil and the pollution of our soil, water, and atmosphere. The earth's size and resources are so great that the effects of deterioration are insidious rather than dramatic. In contrast with the immediate benefits from such exploitation, apprehension about longer range detriments often loses out.

Individual maturation always involves learning how to postpone immediate gratification for the sake of longer range benefits. We do this when we invest years in education or when we protect our families with insurance. Yet, many prudent people (patients and doctors alike) smoke, drink, overeat, abuse drugs and indulge in serious risk taking behavior at work or at home. In each case the immediate consequences are gratifying while the longer range ones seem improbable, even though they may be deadly when they occur. This paradox exists in all of us. Live for today, but plan for the future.

Socially we may be even less mature than we are individually. In order to maintain our living standard and to compete with other nations, we cut corners in industrial safety and in the disposal of toxic wastes while we simultaneously deplete and poison our beautiful land. The ultimate absurdity is demonstrable in the nuclear energy industry where for the sake of cheap electricity we engage in producing fissional by-products we do not know how to dispose of safely. Needless to say we are also producing nuclear weapons whose use in war will so badly pollute the environment with radionuclides and soot generated by the burning of cities that civilization as we know it and perhaps life itself will become extinct.

American medicine is in a tumultuous state. On the one hand, it is becoming more industrialized and dependent upon high technology. On the other hand, it is increasingly concerned with health promotion and disease prevention rather than the ''fix it'' medicine which has been our preoccupation for so long. Health promotion and disease prevention require vigilant concern for the deteriorating and dangerous environment in which we all live. The modern physician is broadly trained in the natural, biological and behavioral sciences. Moreover he encounters daily the pain and death that is associated with indulgence and abuse of the self or the environment. Like everyone else he has the need for daily gratification and must endure some daily frustration. Nonetheless, he is equipped professionally to understand the problems of maintaining a healthy environment and ecological balance. Properly he should take active leadership in considering these matters.

From Dr. Charles I. Sheaffer, a pediatrician in Chapel Hill.

I think this is an interesting question and have not previously given much thought to it. Perhaps an open statement encouraging programs such as those sponsored by North Carolina Wildlife Federation, perhaps encouraging school projects, and perhaps giving an award to the grade school which gives the most innovative approach to ecology and pollution. In summary, I would favor supporting and giving credit to individuals who are approaching ecology and pollution reasonably.

- EDITOR'S NOTE:

I have always been curious about how we view the difference between the public's health and the health of a single individual. They seem to be intimately related but we have tended to split them. Expertise in the two areas requires different training. Physicians get to be pretty good in dealing with individual health but don't feel as expert when it comes to dealing with the public's health. If our Forum's writers are correct, we need to blur the margins between public and private health and become expert at both. The issues are too important to ignore.

For the next Forum question I would like to hear your opinions on a different issue. **Plumbers and electricians are paid for their services by the hour in a perfectly acceptable fashion. Should doctors also be paid for time spent with patients? If so, should this be controlled?** Please send your response by June 21 to Eugene W. Linfors, M.D., Box 3381, Duke University Medical Center, Durham 27710.

Terminal Illness Management Electives — The Establishment of a TIME Committee

Charles A. Speas Phillips, M.D.

• *The role of a TIME committee in the living of your last days.*

Fear of Death

For the majority of people, the fear of death[1] is less terrifying than the fear of the way in which one dies. Religion may provide relief from the fear of death, but the events that precede death will remain unknown until their occurrence. Will death be sudden? due to a heart attack? a paralyzing stroke? Or will death come slowly? be due to cancer? be prolonged, painful, expensive, and deplete family resources?

Decisions concerning death tax the healthy mind. Good decisions may escape the mind burdened with pain, agony, concern about loved ones to be left behind, or a body suffering indignities of tubes, catheters, pulmonary ventilators, etc.

It is therefore important to have a plan for this period,[2] as outlined in a "living will"[3] or thru a proxy[4] designated to make decisions. Good decisions will be made most frequently when accurate, current, and full knowledge is available. Patients, families, and frequently physicians need help — information and moral support — in arriving at the best decision, one that is most appropriate for the period of terminal illness, and one that will leave little guilt feeling thereafter.

Physician, family and/or patient rarely gain from "protection from the truth."[5, 6] The risk of withholding facts of diagnosis, prognosis and treatment alternatives from the patient is great for it denies the patient the autonomy which is rightfully his/hers. Paternalistic decision-making by physicians is fortunately declining rapidly. When obtainable, informed, competent, patient consent is considered essential, or in the absence of competence, informed family or other appropriate consent.

Making the Decisions

Competent adult patients should be free to make decisions after obtaining adequate knowledge from their physician, consultants and other sources of accurate and timely information. The patient's wishes for the future when he/she may become incompetent can be accomplished, at least in part, through a "living will" or by appointing a proxy. Many states have statutes which recognize "living wills." Certainly, written witnessed statements provide better protection than verbal expressions.

For those who have passed into incompetence, or for children who are not of age, state statutes, judicials decisions, and legal opinions[7] provide guidance as to who should make the decisions for, or withholding of, diagnostic tests, drugs, treatments, or surgery.

Decision makers (patients, parents, proxies, legal guardians, next of kin, etc.) should be free to exercise their responsibility with their physician *without* interference from government, "do gooders" or courts. Outside interference has been reported frequently as in the case of Quinlan,[8] "Baby Doe"[9] and others.

The position of the AMA, opposing government participation in the responsible party-physician relationship, was made clear in a statement issued in April 1983.[10]

The responsibilities of physicians to the terminally ill are well known and were reviewed recently by a group of renowned physicians.[4]

Jackson and Younger[11] have pointed out some clinical situations in which precautions must be used to avoid pre-empting the patient's right to make decisions.

Some Problems of Concern to the Terminally Ill and Their Families

Some principal concerns to be addressed in the terminal period are:

1. *Seeking the "needle in the haystack"* — wandering elsewhere looking for promise of a cure after the family physician has honestly informed the competent patient and/or family that there is little hope of cure or improvement.
2. *Prolongation of agony* — continuing the use of diagnostic tests and treatments that offer little or no chance of improving the quality of life or reversing the course of the terminal illness.
3. *Relief of pain*[12] — when the finality has been identified, withholding of pain relief has no place in medicine, even with danger of addiction.
4. *Indignities* — continued use of IVs, tube feeding, gastrostomies, pacemakers, catheters, etc., which prolong and may increase agony and suffering should be assessed to evaluate improvement in the quality of life they may provide.
5. *Wiping out of family resources* — understood, the patient's welfare is paramount. Yet how often have useless treatments been carried out without offering the patient improvement in quality or significant prolongation of life,

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From Pinehurst Professional Center, 165 Page Road, Pinehurst 28374.

only to wipe out family resources, often to the point where the family exists at poverty levels or education is denied the children?

How to Help the Patient. The TIME Committee[13-16]

The hospital in its bylaws should establish a TIME committee. The word TIME is the acronym for *T*erminal *I*llness *M*anagement *E*lectives. This patient service committee establishes policies and resources for the optimum care of hopelessly ill patients. It is composed of interested persons from the community, a variety of physicians — family physician, surgeon, oncologist, radiation therapist — floor nurse, clergyman, lawyer, social worker, and representatives from home care agencies and hospices. The TIME committee identifies interested persons and defines policy and procedures which provide information and moral support. The members of the committee are a resource for the patient and family and physicians who need information and moral support.

The TIME committee should establish ways for persons on the staff to be available to:

1. Assess family problems and concerns, resources, goals and patient competence.
2. Assimilate various alternatives for the patient and family.
3. Counsel with the patient and family to provide information on diagnostic procedures, treatment modalities and procedures such as chemotherapy, irradiation therapy, surgery, resuscitation[17] or not, and levels of treatment facilities such as acute care, skilled nursing care, long term care, rest home, home care, and/or hospice care.
4. Establish policies for administration of "living wills" or use of a designated proxy.
5. Establish reasonable criteria for withholding treatment including resuscitation — DNR[18] (Do Not Resuscitate). Such criteria would include at least an established diagnosis for a fatal illness which is in a terminal and irreversible state such as coma.[19] A written DNR policy should be developed and have hospital staff approval.
6. Additional responsibilities might include the education of patient and staff concerning applicable laws and policies that relate to assessment of competence, definition of death, guidelines for procurement of organ donors, and guidelines for harvesting organs for transplant.

Patients, families, and physicians are most likely to make the best decisions in the period surrounding death with full knowledge of diagnosis, treatment alternatives, and prognosis. The estabishment of TIME committees is encouraged to develop policies and procedures for assistance through information and moral support to those persons making difficult decisions.

The exact role of technology, compassion, sanctity of life or quality of life,[20] access to care, resources available, and legal precedents change rapidly with time, but with experience and knowledge, we may arrive at a point in the future when we may look forward to comfort and dignity and freedom from fear and pain during our last days.

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Medical Revolution — Hospital Crisis

John F. Lynch, M.D.

- *The Chairman of the North Carolina Medical Care Commission updates us on medical and hospital progress in recent years.*

CONTROL of large segments of infectious disease, fantastic strides in public health (clean water, pasteurized milk, sewage disposal, etc.), nutritional successes, development of specific treatments for many diseases — these are a few of medicine's achievements in the last hundred years. They have allowed us to enjoy an unheard of degree of comfort, security, and good health.

This medical revolution has been accomplished through a vast effort by our whole society. In North Carolina our public sector has joined in this effort through hospital programs and unlimited support.

In the 1940s, a "Good Health" program was conceived and successfully initiated our present hospital program. Mr. Kay Kyser spearheaded the effort. We did not have hospitals that were adequate. Our goal was hospitals in every community where one could be supported. Our basic guideline was four hospital beds per 1,000 population. Since that campaign, over 40 years ago, these objectives have been largely accomplished.

The hospitals of that day were not very sophisticated. Most of today's ultramodern technology was unknown.

Progress has radically changed the above concept. World War II diminished the length of hospital stay. We found it was not necessary to keep sick people in bed for long periods. We found that they did better if they got up sooner, and bed rest has continued to shrink as a necessary part of convalescence. Gradually a great variety of factors altered the balance between hospital care and ambulatory care. Not only did the length of hospital stay shorten but the number of hospital days per 1,000 persons decreased.

Other marks of progress:

Medical:

1. Better medical and drug treatment of disease.
2. Better surgical techniques and pre- and postoperative care.
3. Day surgery (in California, as much as 60% of surgery is day surgery; in North Carolina 30%).
4. Development of intensive care units (CCU, ICU, intensive care nurseries).
5. Emergency room coverage (full-time).
6. Emergency medical service with transportation: ambulances, helicopters (one of our great strides).
7. New diagnostic and treatment techniques — invasive and non-invasive (CAT scanners, radiology, mechanized laboratory, etc.).
8. Surgicenters.
9. Birth centers.
10. Urgent care centers.
11. The pill.
12. Legalized abortion with abortion centers.
13. Preventive care programs, as in daily public health activity.
14. Better care of aging population, nursing homes, life care centers, and so on.
15. Transplantation of hearts, lungs, livers, and kidneys.
16. Mechanical hearts for temporary support and for long-term support.

Economic and Political:

1. Decreasing coverage for in-hospital patient care from medical insurance, government programs, and corporate medical benefits.
2. HMO, PPO, etc.
3. Inflation with huge increase in cost.
4. Technological advances with demand for ultimate care for every patient.
5. Increased standard of education and living.
6. Entitlement programs.

With these and many other factors, hospital usage continues to go down. Modern technology and advances have greatly increased the use rate of hospitals; this is more true in full service hospitals than smaller ones, but length of stay has diminished unbelievably. The services now given in the hospital are more expensive and more sophisticated. North Carolina faces quite a dilemma. We have 26,000 general hospital beds. Currently on any day of the year almost 10,000 are empty. Hospital bed occupancy in North Carolina went down 10% in 1982 and 10% in 1983. It probably went down equally as much in 1984.

With all these events and facts, it is not much of a mental exercise to see what is happening to hospital usage. Also in North Carolina we have several hospitals (currently breathing their last) with practically no patients, and they are approaching bankruptcy. In addition we have a number more with a patient census so low they cannot justify staying open and generally are in deep financial trouble. Hospital financing today is a universal problem.

This is a critical problem and demands good common sense solutions.

As is obvious, the old small general hospital in every

From 905 Arbordale Drive, High Point 27260.

community no longer fits the medical needs of our population. Since World War II, the character of hospitals has changed. Generally, a hospital was a hospital. In reality, a 50-bed hospital was a miniature medical center. In other words, all hospitals, with some exceptions of course, did essentially the same thing. This has changed drastically and we can now identify distinct levels of service that various categories of hospitals provide.

Perhaps it should be pointed out that the closing of beds in small, financially troubled hospitals may not be the worst thing in the world that could happen. Rather than have an underfinanced, understaffed, behind-the-times hospital, a community could use its resources to better advantage by developing alternatives to hospitalization. Such things as urgent care, convalescent care (nursing homes), group practice, ambulatory surgery, rural health clinics and a good medical transportation system are suggested. Leave the heavy stuff to well established hospitals. The more sparsely populated areas may be able to develop excellent alternatives but not afford a full-blown hospital.

This is going to be traumatic and will demand everyone's best efforts. People must work together who never have before. Hospitals are usually one of a community's biggest industries, with a large number of employees. Hospitals are a source of great civic and political concern and pride. Like schools, medical care is considered when relative desirability as a place to live is evaluated. Truly, these decisions are going to take all our mutual understanding and cooperation as well as love and compassion.

As if this were not enough, the "medicine revolution" is just beginning. In our immediate future we will see changes the average person can barely comprehend, but they are here.

Soon, many hereditary diseases will be corrected or prevented by genetic engineering. Cancer will be cured by early diagnosis and early treatment with techniques being developed, one of which the media have termed the "silver bullet." All mental disease will be treated medically. Preventive medicine will vastly improve.

We will regularly do a mini-physical examination for ourselves at our breakfast table, with our personal computers, then have an answer per computer. Here we can each morning do our own urinalysis, blood pressure, many chemical analyses (blood sugar, cholesterol, etc.) and test for many different early forms of cancer.

Yes! The revolution has barely begun. It is fantastic and exciting. It is going to take the best of all of us.

The medical profession, as represented by the North Carolina Medical Society, and many allied sciences, as well as all of society should not be bashful. They should all stand up and take a gracious bow. Then we must all lend our best efforts to correcting the rough spots as these great new programs and improvements in life evolve.

The following letter, sent to new members of the North Carolina Medical Care Commission by its Secretary, explains the role and activities of the Commission.

Governor Martin's office has advised us of your appointment to The North Carolina Medical Care Commission and has asked that you be furnished information regarding the Commission's activities.

The Medical Care Commission was created largely as a result of a finding of a special commission, the North Carolina Hospital and Medical Care Commission. This Commission was appointed in 1944 by Governor Broughton to study the critical shortages in general hospital facilities and trained medical personnel in the State, and to make recommendations for improvements in these areas. Among recommendations which were made was a proposal that the legislature provide for a permanent state agency responsible for the maintenance of high standards in North Carolina's hospitals, administering a medical student loan fund, and a statewide hospital and medical care program.

When the 1945 General Assembly established the Medical Care Commission, it followed closely the proposals of the North Carolina Hospital and Medical Care Commission. Enabling legislation authorized the Commission to:

1. Make a survey of the hospital resources in the State and to formulate a statewide program for construction and maintenance of local hospitals, health centers and related facilities, and to receive and administer Federal and State funds appropriated for such purposes.
2. Make loans to students who wish to become physicians.
3. Survey all factors involved in the location of the expanded University Medical School. (The same act authorized the expansion of the UNC Medical School from a two-year to a four-year school.)
4. Several other activities which are not now included in the Commission's responsibilities.

In writing this enabling legislation, the General Assembly accurately anticipated the Federal legislation that was to come a year later. In 1946, Congress passed the Hill-Burton Act and the Medical Care Commission met all Federal requirements and was designated as the state agency authorized to administer the program within North Carolina. Since 1946, health facility construction in North Carolina under the Hill-Burton program has totaled more than $500 million, of which 40% was financed with Federal funds; 5%, State; and 55% local. Of the more than 500 Hill-Burton projects, 241 were general hospital projects, including 80 all-new facilities. As you may know, the Hill-Burton program was incorporated into the National Health Planning and Resources Development Act of 1974. Since that time, Congress has not appropriated additional funds for construction.

Since passage of the Executive Organization Act of 1973, The North Carolina Medical Care Commission has functioned under the Department of Human Resources and consists of 17 members. Three are nominated by the State Medical Society, one by the State Pharmaceutical Association, one by the North Carolina State Nurses' Association, one by the North Carolina Hospital Association, and one by The Duke Endowment. These nominations are subject to approval of the Governor. In addition, 10 members, one of whom by law must be a dentist, are appointed by the

Governor.

Today the Commission is responsible for the governance of eight programs:

1. the licensure of hospitals;
2. licensure of outpatient surgical facilities;
3. licensure of nursing homes;
4. licensure of home health agencies;
5. licensure of hospices;
6. the regulation of ambulances and emergency medical services personnel;
7. the issuance of revenue bonds for the construction of hospitals and related facilities;
8. certification of freestanding abortion clinics.

The 1975 session of the General Assembly enacted the Health Care Facilities Finance Act (G.S. 131A) which authorized the Medical Care Commission to issue its tax-exempt revenue bonds and to lend proceeds from the sale to finance construction projects. To become eligible for tax-exempt status, a hospital must deed all properties affected by the project to the Commission. After financing, the Commission may lease the facility to the hospital for operation, sell the facility back to the hospital or accept a mortgage on the property. In any event, the hospital regains title to the properties after the bonds are retired.

Under this program, the Commission has authorized approximately $335 million for construction projects. In addition, projects amounting to more than $230 million are in the planning process. The Facilities Finance Act has become the major vehicle for obtaining capital funds for nonprofit institutions.

In 1973, the General Assembly passed the Emergency Medical Services Act of 1973 which greatly expanded the responsibility of State Government in the area of EMS. This act vests responsibility for the development of a comprehensive program in the Secretary of Human Resources and authorizes the creation of a statewide EMS program. This legislation reaffirms the State's regulatory role by requiring inspections of ambulances, the issuance of permits for the operation of ambulance vehicles, and the certification of ambulance personnel. Authority was given to the Medical Care Commission to promulgate rules and regulations necessary to carry out the governance of ambulance services.

The Commission regularly meets the third Friday of the last month of each quarter. The next meeting is scheduled for June 21. An Executive Committee meeting is usually held on Thursday evening prior to the Commission meeting of Friday morning. All members are reimbursed for travel expenses and subsistence subject to the limitations prescribed by G. S. 138.5. In addition, a per diem payment is made in the amount of $15.00.

Names and Addresses of Current Members of the Commission

Members	Address	Original Appointment	Term Expires
John F. Lynch, Jr., M.D., Chairman	905 Arbordale Road High Point (27262)	1972	June 30, 1987
Thomas R. Howerton, Vice-Chairman	The Program on Access to Health Care P. O. Box 10937 Raleigh (27605)	1965	June 30, 1988
Gwendolyn Blount	1224 Eastside Drive Greensboro (27406)	1984	June 30, 1986
Jack L. Church, M.D.	942 Norwood Street Lenoir (28645)	1982	June 30, 1986
Jack V. Hill, D.V.M.	2126 Hope Mills Road Fayetteville (28304)	1977	June 30, 1985
James A. Johnson, M.D.	P. O. Box 5708 High Point (27262)	1977	June 30, 1985
David A. Jones	2054 Cynthia Drive Mount Airy (27030)	1980	June 30, 1988
Billy G. McCall	The Duke Endowment 200 S. Tryon Street, Suite 1100 Charlotte (28202)	1977	June 30, 1985
Daniel D. Mosca	Hillhaven Regional Office 3801 Old Wake Forest Road Raleigh (27609)	1983	June 30, 1987
Tom Paxton Phillips	3101 Sharon View Road Charlotte (28210)	1980	June 30, 1987
Mary Edith Rogers	1264 Queensgate Gastonia (28052)	1978	June 30, 1986
W. Lewis Sauls	Courthouse Square Whiteville (28472)	1984	June 30, 1985
O. R. Stovall, D.D.S.	304 Bunche Drive Goldsboro (27530)	1980	June 30, 1987
Kathy Arnold Taft	611 Queen Anne's Road Greenville (27834)	1984	June 30, 1988
David T. Tayloe, M.D.	608 East Twelfth Street Washington (27889)	1973	June 30, 1985
William H. Wilson	2000 Fairview Road Raleigh (27608)	1974	June 30, 1986
Louie E. Woodbury, Jr.	Post Office Box 270 Wilmington, N. C. 28402	1984	June 30, 1988

Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

June 19
Cutaneous Manifestations of Systemic Illness
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

June 20
Crisis — Then & Now
Place: Elizabeth City
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

June 23-28
NC Health Promotion Wellness Institute
Place: Raleigh
Credit: 27 hours Category I AMA, AAFP
Fee: $260-370
Info: Jacqueline Rollins, Wake AHEC, 3000 New Bern Avenue, Raleigh 27610. 919/755-8018

July 5-7
15th Annual Sports Medicine Symposium
Place: Wrightsville Beach
Info: Alan Skipper, NCMS, Box 27167, Raleigh 27611. 919/833-3836

July 11
Crisis — Then & Now
Place: Hickory
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

July 15-19
Sonography of the Abdomen
Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: Dianne L. Willard, Bowman Gray, Winston-Salem 27103. 919/748-4505

July 16
Crisis — Then & Now
Place: Wilson
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

July 17
Diabetes/New Care Concepts
Place: Sanford
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

July 29-August 3
Diagnostic Imaging
Place: Atlantic Beach
Fee: $350
Credit: 18 hours Category I AMA
Info: Carl E. Ravin, M.D., Box 3808, Duke University Medical Center, Durham 27710. 919/681-5268

OUT OF STATE

June 27-29
Bones, Joints, and Sports Injuries
Place: Virginia Beach, VA
Fee: $275
Info: Beth Winn, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

July 1-6
Mid-Summer Family Practice Digest
Place: Myrtle Beach, SC
Fee: $300
Credit: 30 hours AAFP
Info: NCAFP, Box 20146, Raleigh 27619.

July 19-21
5th Annual MCV Cardiology Conference
Place: Hot Springs, VA
Fee: $275
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

New Members

ALAMANCE-CASWELL
Wayne Kimberly Ruth (PUD), 327 Graham-Hopedale Road, Burlington 27215

BEAUFORT-HYDE-MARTIN-WASHINGTON-TYRRELL
Edward Feldin Hill (FP), 501 W. 15th St., Washington 27889

BUNCOMBE
Harry G. Burton, III (CDS), 17 Brookside Road, Asheville 28803

BURKE
William Townsend Freeman (AN), P.O. Box 2245, Morganton 28655

CUMBERLAND
Norman Irwin Snyder, 3425 Melrose Road, Fayetteville 28304
Douglas Wayne Whetsell (IM), 1756 Metromedical Dr., Fayetteville 28304

DURHAM-ORANGE
Carl Elving Anderson (Resident), 1702 Vista St., Durham 27701
Abdullah Onsy Askar (Resident), 2748 Middleton Ave. 15-H, Durham 27705
Gregor George Cleveland (Student), 114-A High Street, Carrboro 27510
Elizabeth Jane Engelhardt (student), 418 Ridgefield Road, Chapel Hill 27514
Hratchia Havoundjian (student), 4545 S. Chelsea Lane, Bethesda 20874
Hector Jesus Hidalgo (DR), 2609 N. Duke St., Durham 27704
Victor Wei Ho (student), 801-B Watts St., Durham 27701
Bettina Bass Meekins (resident), 6 Saint James Court, Durham 27713
Herbert Charles Pfaff (student), 1204 N. Gregson St., Durham 27701
James Scott Rankin (CDS), Box 3851, DUMC, Durham 27710
Bennie Dwayne Roberts (student), 1119 Hillcrest Dr., Chapel Hill 27514

Marc Scott Schwartzberg (student), 6-A Estes Park Apts., Carrboro 27510
Kassell Eugene Sykes, Jr. (student), G-11 Estes Park Apts., 306 Estes Dr., Carrboro 27510
Jo Marlene Travis (student), 1340-5 Ephesus Church Rd., Chapel Hill 27514

EDGECOMBE
Steven Seth Leblang (FP), P.O. Box 688, Pinetops 27864

FORSYTH-STOKES-DAVIE
David Craig Apple (student), 624 Westend Blvd., Apt. #5, Winston-Salem 27101
Dewey Herbert Bridger, III (student), 2518 Weymouth Road, Winston-Salem 27103
Steven Ping Chan (student), Medical Student Box 91, Bowman Gray Medical School, Winston-Salem 27103
Toni Michele Cutson (FP), 8838 Homewood Drive, Clemmons 27012
Andrew Martin Davey (student), 1618 Queen St., Winston-Salem 27103
Kenneth Robert Francis (student), 2353 Salem Court-D, Winston-Salem 27103
Fairfield Goodale (PTH), 300 S. Hawthorne Road, Winston-Salem 27103
Joseph Scott Greene (student), 236 Lockland Ave., Winston-Salem 27103
Kelley Ann Heller (student), 2250 Sunderland Rd., Apt. 19B, Winston-Salem 27103
Bonnie Jean Kerr (student), Box 245, Bowman Gray, 300 S. Hawthorne Road, Winston-Salem 27103
Ernest Paul Phillips, Jr. (CD), 1405 Plaza Drive, Winston-Salem 27103
Lea Harding Rayman (student), 1840 Elizabeth Ave., Winston-Salem 27103
Anthony Richard Riela (resident), 4300 Mill Creek Road, Winston-Salem 27106

GASTON
Karl Joseph Schmitter (GS), 902 Cox Rd., Ste. 6, Gastonia 28054

GUILFORD
Donald Joe Digby (OPH), 3312 Battleground Ave., Greensboro 27410
Salvatore John Pelligra (PM), 3033-B Pisgah Place, Greensboro 27408

IREDELL
Michael Avery Kepley (OBG), 750-H Hartness Rd., Statesville 28677

JOHNSTON
John Francis Ivan Zeedick (AN), P.O. Box 1950, Smithfield 27577

MCDOWELL
Lawrence Stanley Rosen (U), Route #1, Box 2312, Old Fort 28762

MECKLENBURG
Danny Edward Huntley (FP), 7128-B Albemarle Road, Charlotte 28212
John Peter Santamaria (resident), 1540 Garden Terrace, Apt. 208, Charlotte 28203
James Neil Shearer, 2711 Randolph Rd. Ste. 507, Charlotte 28207

MOORE
Thomas Raymond Kearney (P), 140 S.W. Broad St., Box 56, Southern Pines 28387

NEW HANOVER-PENDER
Kenneth Marburg, 343 Bradley Dr., Wilmington 28403
John Lauren Remington (R), 2101 S. Live Oak Parkway, Wilmington 28403

ONSLOW
George Henry Reichling (D), 224 Memorial Dr., Jacksonville 28540
Pirkko Esteri Reichling (GP), 224 Memorial Dr., Jacksonville 28540

PITT
Jennifer Anne Coats (student), 2603 Crockett Dr., Greenville 27834
John Frederick Holter (IM), Highway 64 West, P.O. Box 310, Bethel 27812
Christopher Jones (student), #4 Wildwood Villas, Greenville 27834
William Paul Lavietes (student), 1809 E. Fifth St., #14, Greenville 27834
Winslow Britt Melvin (student), 108 N. Elm St., Greenville 27834
Walter James Metzger (AI), Dept. of Medicine, ECU School of Medicine, Greenville 27834
Zane Thomas Walsh, Jr. (student), 106 Greenway Apts., Greenville 27834
Bruce Wilhelmsen (ORS), 117 Medical Drive, Greenville 27834

RANDOLPH
Edward Decker Haak, Jr. (IM), 208 Foust St., P.O. Box 2839, Asheboro 27203

ROCKINGHAM
Ayyaz Mahmood Qureshi (IM), 505 N. Third Ave., Mayodan 27027

RUTHERFORD
John Jefferson Carter, Jr. (P), City Rt. #3, 311 Fairground Rd., Spindale 28160

WAKE
George Sadler Edwards, Jr. (ORS), 3410 Executive Dr., Raleigh 27609
Linda Chappell Mohr (OBG), 1100 Dresser Court, Raleigh 27609

WAYNE
James Norman Atkins (HEM), 201 Cox Boulevard, Goldsboro 27530
Thomas Marvin Knutson (EM), P.O. Box 10867, Goldsboro 27530

Letters to the Editor

More on Tails of Woe

To the Editor:

Dr. Frazier's scientific article, "Coccydynia: A Tail of Woe," (NCMJ 1985;46:209-212) is a very well written, interesting and informative paper. I congratulate her. The four illustrative cases were well selected and are most appropriate.

Having seen and treated several hundred people with this disorder, I have had some interest in it. The mechanical variations and the mechanical aspects of the condition pointed out by Dr. Frazier in her publication need further clarification. The recommended treatment in most of her cases was a foam rubber donut and/or a U-shaped pillow.

I have found that a much better form of treatment is to explain to the patient the nature of this mechanical (and only secondarily inflammatory) problem. As Dr. Frazier mentioned, the abnormal mechanical stress on the sacrococcygeal joint can be removed by having the patient sit up straight so that their body weight rests on their ischial tuberosities and their posterior thighs. This can be achieved by having the person sit on a *firm* seat which is not too low and, most importantly of all, to keep their buttocks in the posteriormost portion of the chair — that is, to keep their buttocks up against the back of the chair.

I feel that the sponge rubber donut and U-shaped pads should be outlawed. The hysteroid patients that were mentioned in Dr. Frazier's article do take this as a "badge" and sometimes use this as a crutch for years. Another category, such as case three, is embarrassed by carrying around a pillow to sit on. The pillow, in itself, does not relieve the mechanical stress. The mechanical stress can just as easily, or more easily, be relieved by proper sitting posture (with the buttocks posteriorly against the seat).

Paradoxically, soft seats are worse than hard seats. If one sits improperly on a hard seat there is discomfort at the time (such as sitting on a hard athletic stadium seat). This discomfort then warns the patients and they have a tendency then to sit more properly. Conversely, if one sits on a low seat, such as on a soft couch, the body's warning system is delinquent in this anatomical area and oftentimes the persons don't have discomfort until some hours later.

Approximately 5% of the several hundred patients that I have seen have been patients who had had a coccygectomy and are still having symptoms. These patients will respond to proper sitting posture, just as will those who have not been operated upon. Conversely, having the surgery and continuing to sit improperly oftentimes does not relieve patients of their symptoms. I have never operated for coccydynia.

Dr. Frazier's point that an appropriate history and physical are necessary needs emphasizing. The pathological processes, such as in case number four, which were proximal to the sacrococcygeal joint will not have the same history in that they will have discomfort at times other than when they are sitting (night pain) and oftentimes will have lower gastrointestinal or genitourinary tract symptoms. Fortunately, these causes of coccydynia are extremely rare.

Persons who use the sponge rubber donuts, etc., and aren't helped will usually then get in the habit of sitting with their weight primarily on one ischial tuberosity or the other. This then causes lumbosacral symptoms.

If a person follows instructions regarding proper sitting posture (with their buttocks against the posterior aspects of the chair and sitting forward so their weight rests on the ischial tuberosities and posterior thighs) they will be relieved of this mechanical discomfort of coccydynia. If persons are not relieved after having been sitting properly for a few weeks, the doctor must then look for some other cause of the discomfort.

Thomas B. Dameron, Jr., M.D.
P.O. Box 10707
Raleigh 27605

To the Editor:

I am grateful to Dr. Dameron for his observations on the treatment of coccydynia. The day that I received his letter we saw another patient with coccydynia. She was a 54-year-old librarian who thought she had "pulled a muscle" from frequent bending over. She had been collecting sea shells during a weekend at the beach and then developed pain "in the tailbone" which spontaneously improved over the next few days. It acutely worsened after riding a stationary bicycle in her exercise class. Her examination was normal except for exquisite pain on palpation of the tip of the coccyx.

We treated the patient by explaining the mechanical nature of the disorder: her coccyx is relatively unprotected because she is a thin woman. She probably traumatized her coccyx during the 3½ hour automobile ride to and from the beach and then she hurt it again sitting on the hard bicycle seat. Bending over to pick up shells was probably not related to the problem. Sitting all day as a librarian may have contributed further subacute coccyx trauma.

We gave instructions on proper erect seating posture and did not emphasize use of a doughnut or U-shaped pillow. As Dr. Dameron correctly pointed out, three of the patients in my article were not helped by a pillow even though the use of a pillow is unanimously recommended in the literature: Case I still has intermittent pain despite using a pillow at work for several years, Case III was not compliant and Case IV had progressive symptoms due to a tumor. Case II did improve while using a pillow during her most acute pain. Our most recent patient was relieved to hear the pathophysiology of coccydynia and felt that with proper seating posture she wouldn't need any further therapy. We'll see her in follow-up.

Linda M. Frazier, M.D.
Lovest T. Alexander, P.A.-C.
Department of Medicine
Duke University Medical Center
Durham 27710

Good Friday, 1985

To the Editor:

(Thank you, dear Lord, that you are in the "life-changing" business.)

A recent (Good Friday, 1985) visit to the tiny, but sparkling, Hope Mills home of Walter and Lille Mae Cain helped me to rediscover what is changing in my life. Walter (age 79) is now totally bedridden and aphasic, but has been lovingly cared for by his wife Lille Mae over the years. With admiration and wonderment, I remember telling Lille Mae in 1977 (when Walter was in the hospital with his last CVA) that "there is no way that you can manage him at home, short of becoming a trained nurse, and turning your house into a skilled nursing home."

Lille Mae smiles when we recall those words together, on one of my home visits (2-3 times per year) to check on another problem (decubitus ulcer, eye infection, bowel problem, bronchitis, etc.) that she has skillfully managed.

Walter is steadily failing, but his bedroom and their home are filled with life and joy, not death. Their life together is filled with the special love that shines through even the dark events of Good Friday.

"This is my commandment, that you love one another, as I have loved you" — John 15:12 *(RSV)*.

Thank you, Lille Mae and Walter, for showing forth this extraordinary love so clearly and forcefully, and sharing it with me.

Tom Woodworth, M.D.
1657 Owen Drive
Fayetteville 28304

Creation and Evolution

To the Editor:

Regarding "Thoughts on the Beliefs of Medical and Religious Institutions" (NCMJ 1985;46:29-32), I have heard from two other people. A physician in town (Greenville) told my daughter Susan that he liked the paper.

A physician in Siler City wrote and said he had read the paper. He invited me to attend a meeting on "Medicine and Society," to be held at the nearby high school and sponsored by the local medical society. I politely declined his invitation. However, it was good to know that the paper was not completely ignored.

I read Dr. Marion W. Griffin's letter to the editor, "Creation vs Evolution" in the February issue of NCMJ, and was amazed. The letter seemed an incongruous combination of correct facts and doubtful assumptions. I don't really know why I was shocked, since this sort of thing has happened often throughout history.

Anyway, his letter stimulated my writing a short article, called "Thoughts on Evolution and Creationism," which I am submitting for publication. I had to write this article; I could not concentrate on my book until I got this subject done with. If you decide to publish my article, and Dr. Griffin would like to reply to it, from my standpoint, he is welcome to do so. It might be a convenient way to halt the debate by allowing both sides to be presented in the same issue.

The editors of the NCMJ did a public service in publishing Dr. Griffin's letter. Far better to allow someone to blow off steam in the *North Carolina Medical Journal* than to start tampering with school textbooks and the education of the next generation.

Albert D. Warshauer,M.D.
1608 East Fifth Street
Greenville 27834

The Editor Replies:

Dear Dr. Warshauer:

As usual, I enjoyed your writing. The points are well taken and presented in an interesting fashion. Most of our audience will agree with your conclusions. You are preaching to the converted.

My suggestion is that you publish in a place where there are more creationists in the readership.

Keep in touch. You are never dull.

I will publish a portion of your letter and my reply.

Eugene A. Stead, Jr., M.D.
Box 3910, Duke Hospital
Durham 27710

STD Follow-Up

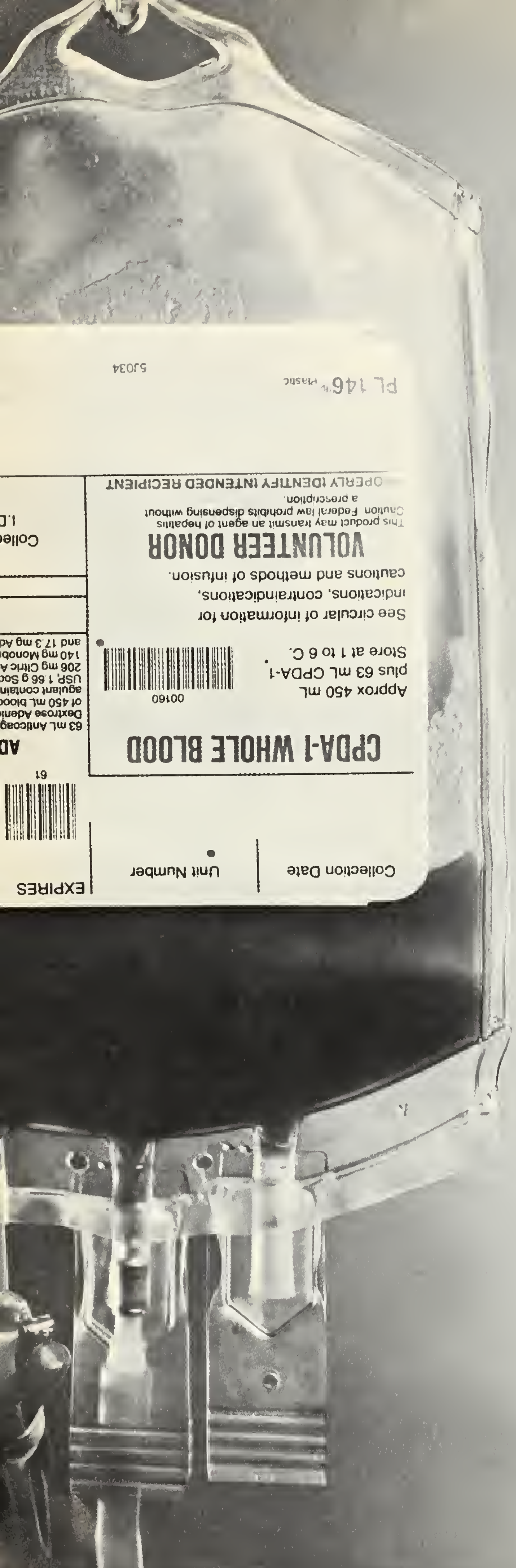
At the North Carolina Medical Society and Auxiliary Convention in early May, both groups recognized the serious epidemic problem of sexually transmitted diseases in North Carolina.

Much interest was generated and I had many inquiries about how a physician could add his/her name to the national referral listing. The VD National Hotline will provide clients who prefer private care and are able to afford it with a listing of private physicians on a fee-for-service, private-patient basis. It is desirable that physicians to whom patients are referred by the Hotline be those with a special interest and continuing education in STD — those for example, who subscribe to and read this journal.

To support this effort by adding your name to the national referral listing you can choose one of three approaches: (1) Call the Hotline Director, at 800-227-8922. (2) Since this line can be very busy, you can call the business number of the Hotline at 415-327-6465. (3) Send a note or post card containing your name, address of your practice, city, state, zip code, phone number, and county to Hotline Director, VD National Hotline, 260 Sheridan Avenue, Suite 307, Palo Alto, California 94306. The card or note should be titled "PMD Resource."

At this time of waning support for public efforts to control STD, the private sector must make a substantial contribution toward solving a health problem that affects so many.

Marguerite K. Tracy
138 Cherokee Road
Charlotte 28207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GENERAL INTERNAL MEDICINE POSITION WANTED. I will complete my residency in September 1985 and am interested in relocating in the Research Triangle area. Call 919/752-0905 or write code 485, NCMJ, Box 3910, Duke University Medical Center, Durham 27710.

GENERAL SURGEON OPENING: to replace retiring surgeon. Excellent location, financial assistance and call exchange available. Contact Grady K. Howard, Administrator, P.O. Box 232, Kings Mountain 28086. 704/739-3601.

FAMILY PRACTICE PHYSICIAN OPENING: Family physician for hospital satellite office in Southern Piedmont North Carolina in the foothills 30 miles west of Charlotte. Guaranteed $72,000 salary or 50% of net whichever is greater — 5 days per week. Contact Grady K. Howard, Administrator, P.O. Box 232, Kings Mountain 28086. 704/739-3601.

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Even Specialists Can Be Useful

Four cases the reader may not have been able to diagnose

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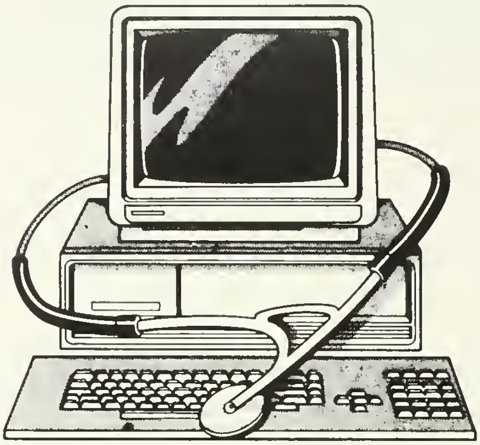

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Cover photo taken by Jeremy Sugarman at the hotel Europa volume 46, no. 7, July 1985

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SCIENTIFIC ARTICLE

A Dermatologist Picks Up the Marbles

Claude S. Burton, M.D.

> *"In the fields of observation [in this instance, a field of poison ivy], chance favors only the mind that is prepared."*
>
> *Quoted by René Vallery-Radot in* The Life of Pasteur *(1927)*

> *"I see no more than you do, but I have trained myself to notice what I see."*
>
> *Sherlock Holmes*

A young lady presented to our emergency room with dermatitis of both feet and distal lower extremities. The left ankle was swollen and hurt with motion. The rash was fire engine red and rare petechiae were scattered here and there in the erythematous lesions. No obvious vesicles were noted but the rash was very wet to touch.

Petechiae and arthritis suggested collagen vascular disease. An ankle film was obtained, laboratory studies were ordered, and preparations were made for joint aspiration. I was asked to see the patient.

The moist, fire-engine red erythema suggested a spongiotic process such as allergic contact dermatitis rather than a vasculitic process. Though there was pain on flexion of the ankle, pounding on the heal and pressure on the joint space produced no symptoms, suggesting that the discomfort was in the skin, not the joint.

History revealed the patient had been target shooting in the woods over the weekend approximately 24-48 hours before the rash appeared. Due to the warm weather, she had been wearing open sandals.

My diagnosis of poison ivy dermatitis met with some suspicion in the emergency room. Having learned from Alexander Fisher that the toxic catecholamines in poison ivy oxidize to an indelible black ink, I examined her jeans and asked if she were wearing them on her shooting expedition. She said that this was not the pair and when I explained why I asked, she and her girlfriend said that the pair she had been wearing while shooting over the weekend were covered with black spots distally which they had assumed to be tar! Vigorous washings had failed to remove the stains.

Her testimony convinced the consulting physicians; the laboratory studies and joint aspiration were deferred. She was treated with a short prednisone taper and calamine lotion topically with prompt relief.

Catecholamines oxidize to indelible black inks, a discovery used widely in the laundry business. India marking ink is a good example. The catechols of poison ivy also do this, particularly when the humidity is low since water rapidly hydrolizes the molecule. When the black oxidized catechol is found on the skin or clothing of a patient with allergic contact dermatitis, one can be fairly certain of the offending agent.

From the Division of Dermatology, Duke University Medical Center, Durham 27710.

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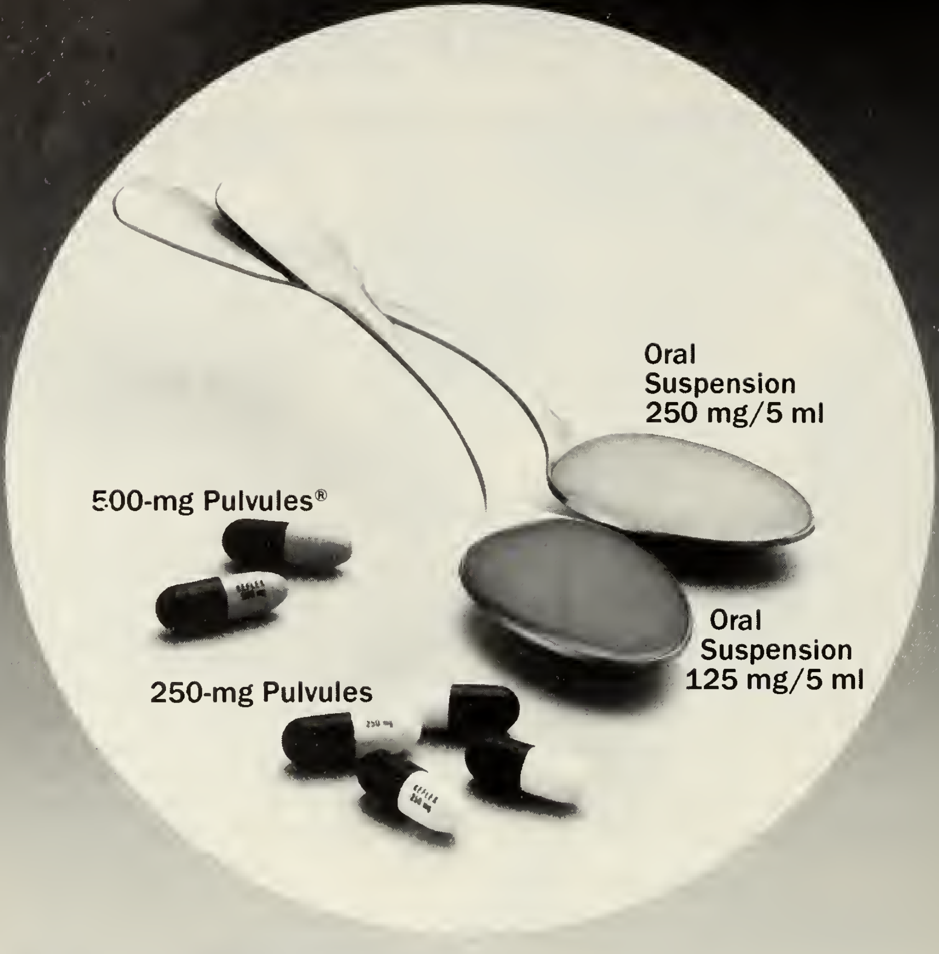

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SCIENTIFIC ARTICLE

Hemochromatosis — An Unusual Arthropathy

John R. Rice, M.D.

- *After 12 years with arthritis, the patient is found to have hemochromatosis.*

THE day-to-day clinical practice of medicine is at times tedious and occasionally graced with the exciting or the unusual. The possibility of finding an exotic disease among the mundane, the pearl among the oysters, is part of the fun and the challenge of our profession as illustrated by the following case.

A 53-year-old white male insurance broker presented with a complaint of ''arthritis'' of twelve years duration. He had been in excellent general health until 1972 at which time he developed acute, painful swelling in the right knee. The knee was aspirated, without examination of the joint fluid for crystals, and injected with corticosteroids with immediate relief of symptoms. Hyperuricemia was found on laboratory testing, a diagnosis of gout was presumed and allopurinol therapy was initiated. One year later an effusion developed in the left knee and was treated in similar fashion with satisfactory results.

Five years after the episodes of knee effusion, painful swelling developed in the metacarpophalangeal joints of the middle and ring fingers on his right hand. The pain responded initially to local injection but recurred and persisted in spite of attempts at therapy with allopurinol, aspirin and various non-steroidal anti-inflammatory agents. Allopurinol was eventually discontinued. In 1982, ten years after the onset of symptoms, his ankles became somewhat swollen and painful, persistent knee stiffness became an increasing problem and the patient complained of stiffness and discomfort in the left hand in a pattern similar to that seen in the right.

Laboratory studies by his physicians at home had included a rheumatoid factor of 1 : 1280 (RA latex) and mild elevations of liver function studies were attributed to low-grade alcohol consumption. Other than a history of recurring prostatitis and non-specific urethritis in the past there was no history to specifically suggest rheumatoid arthritis, other connective tissue disease or spondyloarthritis. The patient's family history included an episode of podagra in his father and a brother with a diagnosis of hypoparathyroidism established at the Mayo Clinic.

Physical findings were normal with the exception of the joints. Minimal fullness was present over the index and middle metacarpophalangeal joints of the right more than the left hand and a suggestion of soft tissue fullness was present in the left ankle. Other peripheral joints and the spine were unremarkable. There were no subcutaneous nodules present and no skin or nail findings to suggest psoriasis.

Laboratory studies usually obtained in patients with arthritis were normal, including a repeat rheumatoid factor. The serum uric acid had been reduced to 1.8 mgm% by aspirin. Liver function studies were remarkable for a slight elevation in SGOT and SGPT.

Hand x-rays (see figure 1) showed small osteophytes at the metacarpophalangeal articulations of the second and third digits bilaterally. Slight joint space narrowing was present at the third metacarpophalangeal joint bilaterally with a suggestion of associated increase in subchondral bone density in the respective proximal phalanges. Ankle films (not shown) showed minimal degenerative change at the calcaneonavicular articulations bilaterally; the subtalar and tibiotalar joints were normal. Knee films were not felt to be indicated.

Subsequent studies included a serum ferritin value greater than 2000 ng% (normal range in adult males 31-294 ng%) and a serum iron of 238 mcg% with a total iron-binding capacity of 240 mcg%. Liver biopsy (see figure 2) showed marked iron deposition within hepatocytes, most prominent in the portal areas, with only sparse amounts of iron within Kuppfer cells. The changes were consistent with hemochromatosis. At the time of diagnosis there was no skin hyperpigmentation and no evidence of endocrine or myocardial dysfunction. Therapy was initiated with biweekly phlebotomy and non-steroidal anti-inflammatory drugs were continued in hopes of minimizing joint complaints.

Discussion

Approximately 50% of patients with hemochromatosis develop an arthropathy in conjunction with other manifestations of the disease.[1] Joint symptoms most commonly present simultaneously with other manifestations of the disease but may occur a decade or more in advance of other symptoms.[2, 3] Clinical and radiological features of the disease are distinctive enough to allow the alert physician to suspect the diagnosis of hemochromatosis and order tests to establish the diagnosis.

Hemochromatosis is an uncommon disorder characterized by excessive iron absorption in the gut. Evidence points to an autosomal recessive mode of inheritance with an estimated gene frequency of 0.056.[4] Clinical manifestations develop as a result of the gradual accumulation of iron

---

From the Division of Rheumatology and Immunology, Duke University School of Medicine, Durham 27710.

in the parenchymal cells of various organs including the liver, endocrine organs, skin, joints and heart.[5, 6] Approximately 90% of clinically apparent disease develops in men; menstrual blood loss has been postulated to delay or ameliorate the development of recognizable disease in women. Alcohol consumption or heavy dietary ingestion of iron may hasten the onset of symptoms. Most patients present between 40 and 60 years of age with bronze or slate-gray cutaneous hyperpigmentation, cirrhosis and endocrine dysfunction, including diabetes and hypogonadism. Myocardial involvement may produce congestive heart failure. Diagnosis is made by liver biopsy showing, as in the case described above, an abnormal accumulation of iron in hepatocytes. Biopsy late in the course of untreated disease may show cirrhosis. Management centers on the reduction of iron stores through regular phlebotomy with a goal of normalizing serum iron levels and maintaining a hemoglobin level of approximately 11 gm%.[7] If initiated at an early stage of the disease, therapy may prevent hepatic, endocrine and myocardial dysfunction or improve function in affected organs.

The arthropathy of hemochromatosis has been well described by several authors[1, 8-11] since the original report by Schumacher in 1964.[12] The characteristic clinical picture is essentially that of osteoarthritis with an atypical and characteristic pattern.[8] Involvement of the 2nd and 3rd metacarpophalangeal joints with loss of joint space, subchondral sclerosis and osteophyte formation is the single most suggestive finding. Subcortical cyst-like changes may occur and diffuse osteopenia may develop but the characteristic periarticular osteoporosis of rheumatoid and other inflammatory forms of arthritis is lacking as are marginal erosions. Hypertrophic arthritis of the interphalangeal joints, lacking entirely in some patients, is indistinguishable from other more common forms of degenerative joint disease but tends to involve the proximal rather than the distal interphalangeal joints. Large joints including the wrists, elbows, shoulders, hips, knees and ankles may be affected although the earliest changes are usually seen in the small joints of the hand.

The arthropathy of hemochromatosis is similar in many respects to that seen in calcium pyrophosphate deposition disease (CPPD), both the ''idiopathic'' form and that seen in association with a variety of metabolic disorders. In approximately 50% of patients with arthritis and hemochromatosis, chondrocalcinosis may be found on x-ray in locations characteristic of CPPD — the hyaline and fibrocartilage in the knees, the triangular cartilage distal to the ulnar styloid, the fibrocartilage at the symphysis pubis and occasionally in the hips or intervertebral discs.[8, 9] Not all of these patients have joint symptoms. Acute episodes of pseudogout may occur, most frequently in the knees, and hemochromatosis should be part of the differential diagnosis of any patient with either chondrocalcinosis or pseudogout even in the absence of obvious changes in the small hand joints.

The pathophysiology of the joint disease in hemochromatosis has not been well defined. Iron deposition in the synovium is a relatively non-specific finding, having been described in rheumatoid arthritis, transfusion hemosiderosis, hemophilia, pigmented villonodular synovitis and other disorders.[8] Iron accumulation in hemochromatosis occurs, however, in Type B synoviocytes and possibly in chondrocytes in distinction from the above listed diseases in which the deposits accumulate primarily in the phagocytic Type A synovial cells. The occurrence of similar joint disease in experimental animals given a sustained iron overload and in some patients with transfusion hemosiderosis supports the putative role of excessive iron stores in producing the arthropathy of hemochromatosis.[9]

Therapy, as noted above, consists of a removal of excessive iron stores via repeated phlebotomy. Prevention of or improvement in organ dysfunction can be achieved with appropriate management but there is little effect on the associated joint diseases.[11] Loss of chondrocytes, cells with little or no regenerative properties, as a result of the

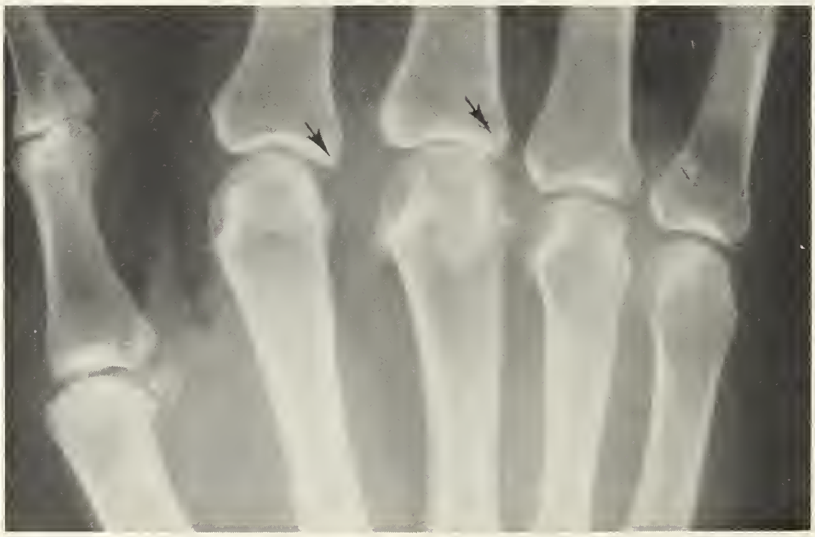

Figure 1. *X-rays of the right hand showing small osteophytes at the second and third metacarpophalangeal joints (arrows) with narrowing of the third metacarpophalangeal joint space.*

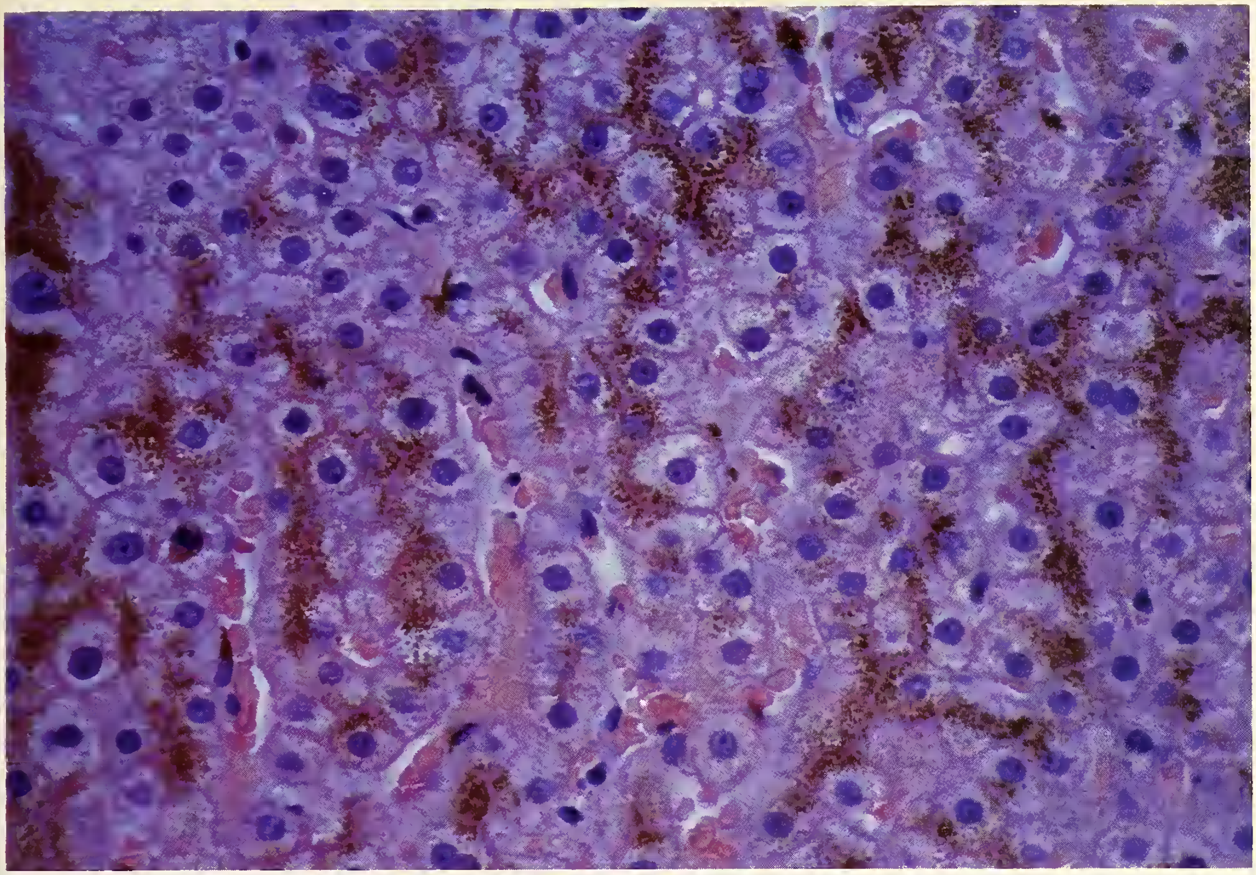

Figure 2. *Liver biopsy showing massive accumulation of iron in hepatocytes with sparing of Kuppfer cells. Special stains (not shown) confirmed the ferrous nature of the deposits.*

toxic effects of iron may account in part for this observation. Iron inhibition of pyrophosphatase has been proposed as an explanation for the occurrence of chondrocalcinosis and pseudogout in some patients.[13]

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SCIENTIFIC ARTICLE

Intermittent Claudication Due to Cauda Equina Compression

James O. McNamara, M.D., Lori Pierce, M.D. and Douglas Slater, M.D.

- *A patient with pain in his legs when he stood, relieved completely when he sat, is cured.*

We recently evaluated a 60-year-old man with an intriguing constellation of symptoms. He was well until one year previously when he developed dull aching pain in his hips precipitated by walking 6-9 blocks. The pain remitted with rest. During the following three months he noticed the pain after walking shorter distances and eventually after merely standing for as long as one minute. The pain would invariably remit within 20-30 seconds after he sat down. The pain was always bilateral, occasionally progressed from the hips to the thighs and even the calves. On one occasion the patient continued to walk in spite of the pain and experienced weakness of both legs and fell. There was no history of pain or weakness elsewhere, nor of bowel or bladder incontinence. There was no history of hypertension, diabetes, or myocardial infarction. The past medical history, family history, and review of systems provided no information essential to understanding the present illness.

The patient's vital signs were within normal limits. His general physical and neurological examinations were also within normal limits. In particular, all of his pulses were full including the femoral, popliteal, posterior tibial, and dorsalis pedis pulses. No bruits were detected. The skin of the lower extremities showed no atrophic changes. Anal sphincter tone was normal. Motor and sensory examinations of the lower extremities were also within normal limits. His muscle stretch reflexes were 2+ and symmetrical and no Babinski signs were present. The responses to both Patrick's maneuver and straight leg raising were normal. At the request of the physician, the patient walked sufficiently far to precipitate his pain; the vascular and neurologic examinations of the lower extremities remained within normal limits in the presence of the pain.

The presence of pain induced by standing and its relief by change in posture together with the negative findings on the vascular and neurologic examinations suggested the diagnosis of intermittent claudication due to compression of the cauda equina. A CT scan of the lumbosacral spine disclosed a spinal stenosis mainly at L3-4; the stenosis was due to narrowing of the bony canal with hypertrophy of the ligamentum flavum posteriorly, and a marked posterior bulging of the L3-4 intervertebral disc anterior to the canal. A myelogram was performed after introduction of metrizamide at the L1-2 interspace. The caudal flow of metrizamide was completely blocked at the L3-4 interspace with the patient in the standing position. The contrast did flow caudally past the block after the patient was placed in the sitting position.

The radiographic findings were confirmed at the time of surgery. A lumbar laminectomy was performed at L3-4 together with removal of the intervertebral disc. The patient's symptoms remitted promptly after surgery.

The term "claudication" is derived from the Latin verb, *claudicare*, which means to limp. The intermittent nature of the symptoms is striking and crucial to the diagnosis, and therefore the term *intermittent* claudication seems appropriate. The vast majority of cases of intermittent claudication of nervous system origin (versus vascular intermittent claudication) are related to compression of the cauda equina. Thus the term "intermittent claudication due to cauda equina compression" seems the most appropriate title of this syndrome and preferable to the popular alternative, "neurogenic claudication."

The precise pathophysiology of the symptoms is unknown. The striking relationship of the symptoms to posture and the stereotyped temporal resolution of symptoms following change in posture are critical clues not only to a neurogenic rather than a vascular origin, but also to the underlying pathophysiology. A variety of degenerative bony and cartilaginous abnormalities superimposed on a developmentally narrow canal (i.e., lumbar spinal stenosis) combine to markedly narrow the lumbar spinal canal. The erect posture presumably precipitates the symptoms because the sagittal diameter of the lumbar canal normally narrows in the extended position and widens in the flexed position. The interaction of physiologic narrowing related to posture together with the pathologic narrowing due to the factors listed above is sufficient to compress the cauda equina. Perhaps compression of the arterial or venous circulation of the root together with the increased vascular demands of nerve tissue (related to exercise or maintenance of the erect position) may interact to produce the symptoms. In any event, surgical decompression leads to prompt resolution of the symptoms in properly diagnosed cases. This outcome provides a happy ending for the patient, the diagnostician, and the surgeon.

From the Division of Neurology, Duke University Medical Center, Durham 27710.

SCIENTIFIC ARTICLE

An Unusual Cause of Recurrent Transient Neurologic Deficit

Marvin P. Rozear, M.D. and Walter G. Wolfe, M.D.

- *A rheumatologist uncovers a rare cardiac condition in a woman with TIAs.*

A fifty-year-old, right-handed bookkeeper was in excellent health until the first week in January 1985. While changing clothes she noted an aching pain in her left arm followed by a rash on the palm and forefinger, which did not blanch. A few days later while talking on the phone, her left hand felt weak and clumsy with tingling which spread into the leg, lasted several minutes and abated spontaneously. The next day she had a splotchy red rash on her hand again. The following week while eating breakfast her entire right side felt numb and weak, her speech became slurred, and she had difficulty getting the right word out for 45 minutes. She had difficulty walking for several hours. The next day she had a slight rash on her right hand. Her internist obtained an EKG, head CT, and an M-mode echocardiogram. She was diagnosed as having vasculitis and was started on Dipyramidole and aspirin. A neurologist examined her and agreed with the treatment. A few days later while dressing she noted ''zigzag lines'' to her left for a few seconds followed by a left-sided headache. This recurred. She noted rash in both hands which came and went, lasting for a few days. On the day of admission she was eating breakfast when she suddenly passed out without warning, convulsive activity or any other specific features. At her local hospital shortly thereafter her examination was normal and she was transferred to Duke Hospital. Her past medical history was unremarkable. She was a nonsmoker and had had no prior symptoms of any cardiac, vascular, pulmonary or neurologic disease.

On examination blood pressure was 110/60 in both arms. Pulse was 70 and regular. She was afebrile. General physical exam was normal except for a cluster of nontender, nonblanching erythematous spots measuring three to four millimeters over the ulnar border of the left palm. Neurologic exam showed mild clumsiness of the left fingers and no other significant findings.

Shortly after the admission she experienced another spell of clumsiness of her right hand and had difficulty speaking which lasted one to two minutes. The rheumatology consultant recommended a 2-D echocardiogram which revealed a 2 x 3 x 2 cm left atrial mass with gelatinous consistency, compatible with a left atrial myxoma.

Because she had experienced another TIA on that day, surgery was recommended immediately, and the myxoma was removed within 6 hours of its diagnosis. The patient tolerated the procedure well, and was discharged with no further difficulties.

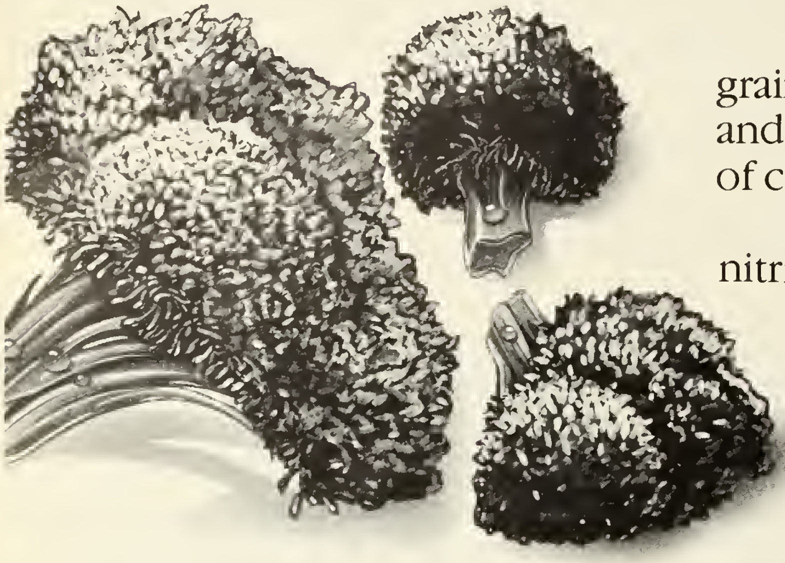
Frequently in the evaluation of cerebrovascular insufficiency the workup focuses entirely on the carotid system. There is some reason for this, as carotid stenosis/ulceration is certainly the most common treatable cause for carotid system TIA. However, when attacks involve both hemispheres intermittently in an otherwise healthy, relatively young, nonsmoking person with or without carotid bruits, other causes must be sought. Cerebral vasculitis is certainly one of these rare causes of cerebrovascular insufficiency.

Atrial myxoma is among the rarest of causes of cerebrovascular insufficiency. In fact it is so rare that some have stated that in a patient with TIAs, if the cardiac exam is normal, echocardiography is not cost effective in the workup. The proponents of this type of thinking might have difficulty convincing this patient or her family of this philosophy.

From the Division of Neurology and Department of Surgery, Duke University Medical Center, Durham 27710.

THIS SPACE CONTRIBUTED AS A PUBLIC SERVICE

A defense against cancer can be cooked up in your kitchen.



There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.

Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash and tomatoes, citrus fruits and brussels sprouts.

Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables, and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods like ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

Be moderate in consumption of alcohol also.

A good rule of thumb is cut down on fat and don't be fat. Weight reduction may lower cancer risk. Our 12- year study of nearly a million Americans uncovered high cancer risks particularly among people 40% or more overweight.

Now, more than ever, we know you can cook up your own defense against cancer. So eat healthy and be healthy.

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See following page for brief summary of prescribing information.

SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related In clinical trials at various doses, the following have been observed

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended The extent to which development of tolerance should modify the dosage program has not been defined *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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SCIENTIFIC ARTICLE

A Big Pain Between The Small Toes

Richard D. Goldner, M.D.

- *The editor's wife had this condition; the author's father cured it.*

MANY of today's medical and surgical publications stress the newest, most sophisticated diagnostic and therapeutic modalities for problems seen most often by the super-specialist. However, we must not overlook other more common conditions that if recognized can be managed successfully without expensive and elaborate tests and procedures.

An example of the latter is the interdigital clavus — a soft corn between the toes. Although a rather mundane topic, our editor has seen several patients in whom this diagnosis was not made until after months of patient discomfort. He was impressed by the simplicity with which this problem could be treated once the diagnosis was made.

Clinical Example

A typical example is a 46-year-old woman who noticed a diffuse, thickened, tender area of skin at the inner surface of her little toe. This had been present for almost a year, and although uncomfortable when she walked, it was most painful when she wore tight shoes.

Examination revealed a reactive proliferation of epidermis at the inner aspect of her little toe. A bony prominence could be palpated beneath this thickened skin and adjacent to it on the fourth toe. Radiographs confirmed that this soft corn was the result of persistent irritation of skin by the irregular base of the proximal phalanx of the fourth toe which compressed the distal end of the proximal phalanx of the fifth toe (figure 1). The skin between these toes was compressed as in a vise and the external pressure resulted in a painful keratosis.

A soft corn (clavus) is the accumulation of horny epithelium between two toes, most commonly the fourth and fifth. Often painful, it is a localized response to pressure or irritation of skin between bony prominences of contiguous toes. The pressure might be between an enlarged condyle of one phalanx and a condyle of an adjacent phalanx (prominent end of one of the bones of the toes), between exostoses (bony spurs) on adjacent toes, or between the base of one proximal phalanx and the adjacent metatarsal head (end of one of the long bones of the foot). The clavus can be present on one toe or "kissing" lesions can be noted on contiguous toes. An early lesion can result from several weeks of compression of the toes either in a shoe that is smaller than usual or by physical activity that results in increased friction between the toes.

At this early stage the lesion can be aborted by wearing a wider shoe (having the shoe stretched) or by using lamb's wool or a small pad to separate the involved toes (figure 2B). These pads are not placed directly over the clavus but are positioned either proximal or distal so as to relieve pressure over the bony prominence. In addition, the accumulated epithelium can be trimmed.

Injection of drugs such as Cortisone and chronic use of sclerosing agents are contraindicated. Mere local excision of the soft corn is fruitless since the causative bony prominence remains.

More definitive treatment consists of excision of the exostosis causing pressure and irritation (figure 2C). It is unnecessary to excise the clavus itself since it will usually disappear after the adjacent bony prominence is removed.

With time, the irritated skin becomes thicker, more

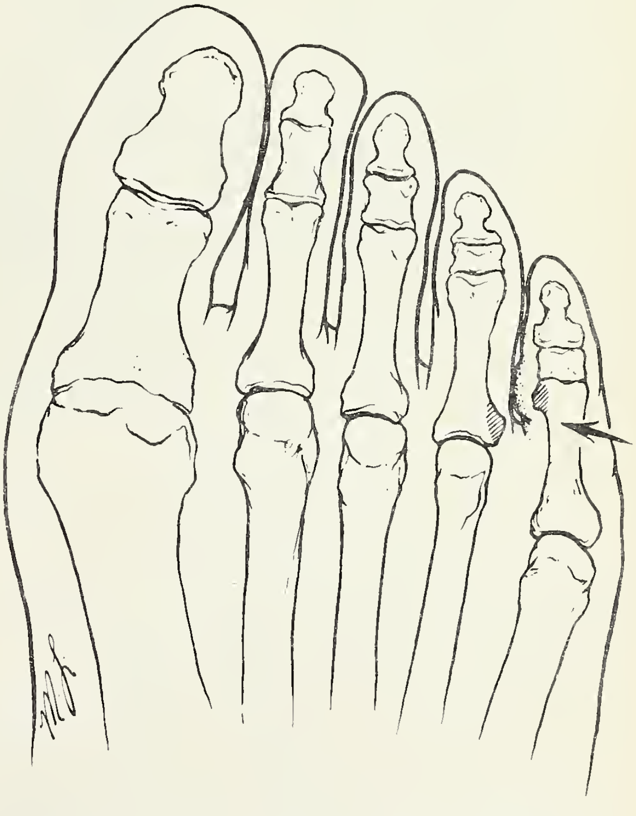

Figure 1. *The outline of the bones of the foot is irregular. Soft corns can form as a response to pressure between any of these prominences on adjacent toes (arrow).*

From the Division of Orthopaedic Surgery, Duke University Medical Center, Durham 27710.

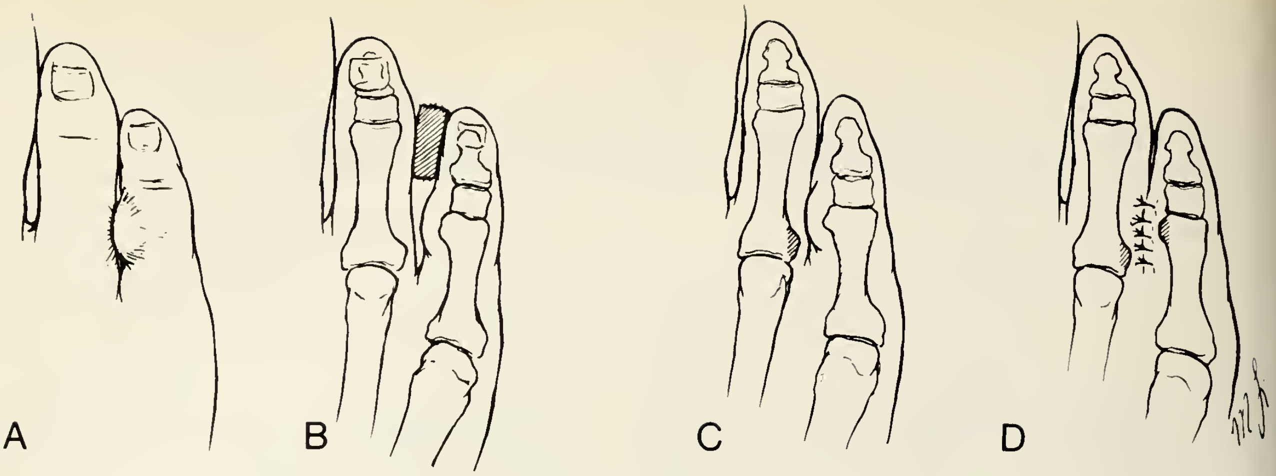

Figure 2. *A. This represents the soft corn (reactive proliferation of epidermis) that has formed as a response to pressure and irritation between irregular bony prominences at the fourth and fifth toes. B. A small pad, positioned distal to the clavus, relieves pressure over the bony prominence and can decrease symptoms in early lesions. C. Bony prominence at the base of the proximal phalanx of the fourth toe (shaded) can be surgically excised to relieve pressure causing the clavus. The clavus itself (on the little toe) will usually disappear after this offending prominence is removed. D. Ultimate treatment is to excise the exostoses at both toes (shaded), to remove the involved skin between the toes and to suture the skin so as to close the involved portion of the web.*

rigid, more painful. The ultimate treatment is to excise the irregular bony prominence causing the pressure, to remove an elipse of skin containing the clavus often between the inner border of the little toe and the inner border of the fourth toe, and to suture the remaining skin (figure 2D). Thus a portion of the web between the two toes is joined (partial syndactyly). By excising the bony prominences and by removing the compressed skin between the two toes, no clavus can form and pain is eliminated.

Although not a complex procedure, the operation should be done when the patient can avoid a great deal of walking, jogging, or wearing snug shoes for at least three months.

Discussion

Treatment is sometimes delayed by failure to recognize the lesion as a clavus. In feet with excessive moisture, maceration can occur between the toes and the soft corn can be mistaken for a fungal infection. Fissures and other skin problems can result from improper use of a variety of drugs. Scar tissue and infection from improper treatment can also complicate the diagnosis.

Although its surgical treatment is not complex, caution must be used in patients with such problems as peripheral vascular disease or diabetes mellitus because healing may be delayed and the risk of infection increased.

The clavus, or soft corn, can be a painful lesion that does not require elaborate diagnostic tests or procedures. It is an entity that should be able to be diagnosed initially by the family physician. If elimination of the lesion is desired an orthopaedic surgeon should be consulted. Although seemingly inconsequential, the diagnosis and treatment require care and caution.

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Please see brief summary of prescribing information on the next page for further details.

Once-daily

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use Effects on plasma volume appear to be minor and somewhat variable INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmias is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient But there are also situations in which sympathetic stimulation is vital For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm

Propranolol is not significantly dialyzable

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

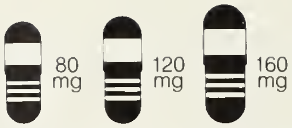
WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures



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INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular bradycardia congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System lightheadedness; mental depression manifested by insomnia, lassitude weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

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SCIENTIFIC ARTICLE

Myocobacterium Avium-Intracellulare and Lung Disease: More of a Problem for Those of Us in the Southeast

Norman Adair, M.D.

- *Close relatives M. avium and M. intracellulare are present most often in the elderly and the immunocompromised, and are very difficult to treat successfully.*

PULMONARY tuberculosis has decreased markedly over the last few decades. As result, there has been a relative increase in the frequency of lung disease caused by the non-tuberculous mycobacteria. Physicians in North Carolina and the southeastern states have long been familiar with non-tuberculous mycobacterial disease of the lungs. In the early part of this century, an ''atypical'' mycobacterium was isolated from patients being treated for tuberculosis at the Battey State Hospital in Rome, Georgia and carried the name of that institution for several decades. We now know the ''Battey'' bacillus as Mycobacterium intracellulare,[1] a close relative of Mycobacterium avium. These two are often grouped together as variants of a single strain. Soil isolates from southeastern river areas yield 100 fold higher concentrations of M. avium-intracellulare (MAI) when compared with soil samples from the northeast.[2] Natives of the southeastern states have an increased frequency of cutaneous reactivity to MAI[3] and an increased incidence of disease due to this organism.

M. avium-intracellulare and M. kansasii account for the majority of the ''atypical'' mycobacterial lung infections. In terms of human pathogenicity these organisms fall between M. tuberculosis, an obligate pathogen, and the benign free living mycobacteria. M. avium-intracellulare can cause an overwhelming and often fatal disseminated infection, especially in the immunocomprised host, e.g., AIDS; however, disease is *usually* manifest as an indolent pulmonary infection in the elderly. The chest x-ray demonstrates infiltrates, often with cavitation, that are indistinguishable from pulmonary tuberculosis.

A confident diagnosis of ''atypical'' mycobacterial lung disease is complicated by the fact that the organism may be a harmless colonizer in the oral cavity or the tracheobronchial tree, particularly in lungs damaged previously by chronic bronchitis or a fibrotic-inflammatory disorder. Strict adherence to diagnostic criteria is especially important when non-tuberculous mycobacterial lung disease is suspected in order to prevent unnecessary and potentially toxic therapeutic intervention. Essential diagnostic criteria for lung disease due to MAI include the repeated isolation of large numbers of organisms from the same source (sputum), the absence of alternative pathogens, and the presence of clinical disease for which no other etiology is apparent. Ahn and co-workers have defined even more rigid criteria[4] based on their observation that patients with sputum positive for MAI may convert to negative with bronchial hygiene alone.

Chemotherapy of M. avium-intracellulare lung disease is often unsuccessful because of primary resistance to most of the first and second line anti-tuberculous drugs. This has prompted some physicians to treat with five and six drug combinations,[5] a strategy analogous to multiple agent chemotherapy of cancer. Presumably, these drug combinations cause multiple metabolic defects which can result in an anti-mycobacterial effect despite high levels of resistance to the individual drugs.[6] Drug toxicity is very common with these regimens. However, some reports suggest that such aggressive therapy may not be required in all cases. Dutt and Stead[7] have reported an initial 80% sputum conversion rate using primarily four-drug chemotherapy. More recent reports from Wales[8] and Denmark[9] indicate 60-70% sputum conversion with a conventional three-drug anti-tuberculous regimen employing isoniazid, rifampin, and ethambutol.

Therapeutic success equal to that currently achieved in pulmonary tuberculosis is not presently in sight and will require improved knowledge of the immunology and biochemistry of M. avium-intracellulare, the development of new drugs, valid *in vitro* susceptibility testing of drug combinations, and additional clinical trials. Current knowledge indicates that initial treatment should include isoniazid, rifampin, and ethambutol. Supplemental chemotherapy should be instituted if there is no sputum conversion in three months or if the clinical situation is deteriorating. Ethionamide and cycloserine are frequently recommended for supplemental regimens. Drug susceptibility testing has not been shown to improve therapeutic response but is often used as a guide for drug selection. *In vitro* studies and preliminary observations suggest that two ex-

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perimental drugs, clofazimine[10] and ansamycin,[11] may be active against M. avium-intracellulare. The latter may be obtained on a research basis from the Centers for Disease Control.[12]

Because of the often indolent nature of these infections, the advanced age of those afflicted, the frequent presence of bilateral involvement, and the coexistence of underlying lung disease, surgery will only occasionally be indicated. However, resection of well-localized lesions, including cavity bearing areas, may be definitive in some cases and should be carried out at a time when available drug effects are presumed to be greatest.

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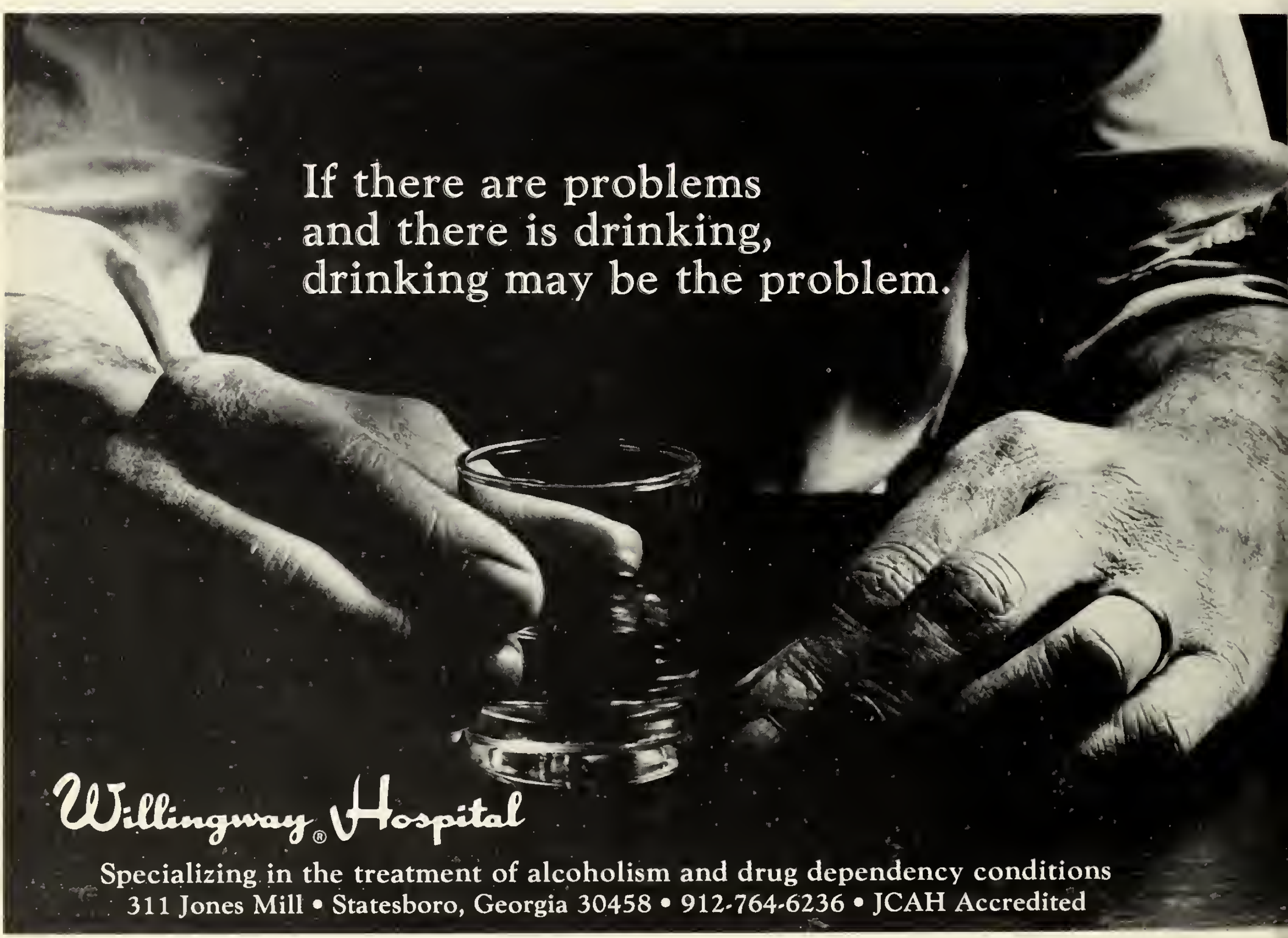

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SCIENTIFIC ARTICLE

Early Diagnosis of Testicular Carcinoma: Self-Examination of the Testicle

E. Everett Anderson, M.D.

- *Cancer of the testis is always treatable and usually curable. Self-discovery is the first and most important step.*

THE incidence of carcinoma of the testis in the United States is 2.2 per 100,000 men. Testicular carcinoma accounts for only one percent of all male cancers; but between ages 15 and 40, the peak incidence of this malignancy, it is the most common solid tumor in men, and between ages 25 and 35 it is the most common cause of cancer death in men. Testis tumors are extremely rare in the black race and unusual in Asians. There is a slightly higher incidence of carcinoma of the right testicle than the left and this could reflect the slightly higher incidence of cryptorchidism on the right side. The cause of testicular carcinoma is unknown. The association of testis tumor and cryptorchidism is well established and there are a few reports of familial incidence. However, no genetic influence on the development of testicular carcinoma has been established.

Since the discovery of cis-platinum in 1974[1] and its subsequent use with vinblastine, bleomycin and other drugs in multiagent chemotherapeutic programs, the cure rate of metastatic testis tumors has dramatically improved. Twenty years ago 95 percent of patients with distant metastases died. Currently the cure rate for patients with distant metastases is 70 percent, and for tumor involving only the testicle and retroperitoneal lymph nodes approximateiy 95 percent are cured. Testis tumor is usually first identified by the patient. Many patients with testis tumors have an antecedent history of scrotal trauma but there is no evidence that testicular trauma can induce malignant changes. More likely, the scrotal trauma causes the patient to examine his testicle and identify the neoplasm. Once the testicular mass has been recognized by the patient, it is frequently misdiagnosed by his physician as epididymitis and delays of effective treatment during antibiotic trials are common. Thirty-five percent of patients will have metastatic disease when the tumor has been identified.

Differential Diagnosis of Scrotal Masses

Scrotal masses can be simply classified as painful and painless. **Common painful scrotal masses** (figure 1) consist of acute epididymitis, torsion of the testis, incarcerated inguinal hernia and torsion of the appendix testis. Acute epididymitis is the most common painful scrotal mass and as a general rule does not occur before puberty. It is often associated with acute prostatitis and previous urethral instrumentation with retrograde vasal dissemination of bacteria into the epididymis. On physical examination the epididymis is significantly enlarged, nodular and tender and there is associated edema but not usually inflammation of the testicle. Manual elevation of the scrotum will alleviate the scrotal discomfort.

Torsion of the testis can occur in utero but the peak incidence is at puberty and it rarely occurs after age 25. In children it may have an insidious onset but in adults it is usually manifest by the acute onset of severe scrotal discomfort. On physical examination, because of shortening of the spermatic cord the testis may be elevated in the scrotum and have a transverse axis. There may be associated edema of the testicle and epididymis. Scrotal elevation does not alleviate the discomfort. Any prepubertal boy complaining of scrotal discomfort should be evaluated immediately for testicular torsion.

An incarcerated inguinal hernia is often associated with a known history of an indirect inguinal hernia and frequently associated with nausea and vomiting.

Torsion of the appendix testis is manifest by the sudden onset of scrotal pain, and physical examination will identify a small "pea-size" tender mass at the superior pole of the testicle. A "blue dot" mass may be visible through the scrotal skin.

Common painless scrotal masses (figure 2) include varicocele, hydrocele, indirect inguinal hernia, cyst of the epididymis and testis tumor. The most common painless scrotal mass is the varicocele which may be identified in approximately 15 percent of men. The longer left internal spermatic vein drains at a right angle into the left renal vein whereas the right internal spermatic vein drains obliquely into the inferior vena cava. Because of this anatomical difference 99 percent of varicoceles occur on the left side. On physical examination the dilatation of the veins in the pampiniform plexus may resemble a "bag of worms."

A hydrocele of the tunica vaginalis is a "bottle shaped" cystic mass. Because of the overlying fluid within the tunica vaginalis the testicle is often difficult to palpate. The thumb and forefinger applied around the spermatic cord at the external inguinal ring will clearly define the upper limits of this scrotal mass and differentiate it from an inguinal hernia. Transillumination will confirm the fluid filled contents and the scrotal mass will be nonreducible.

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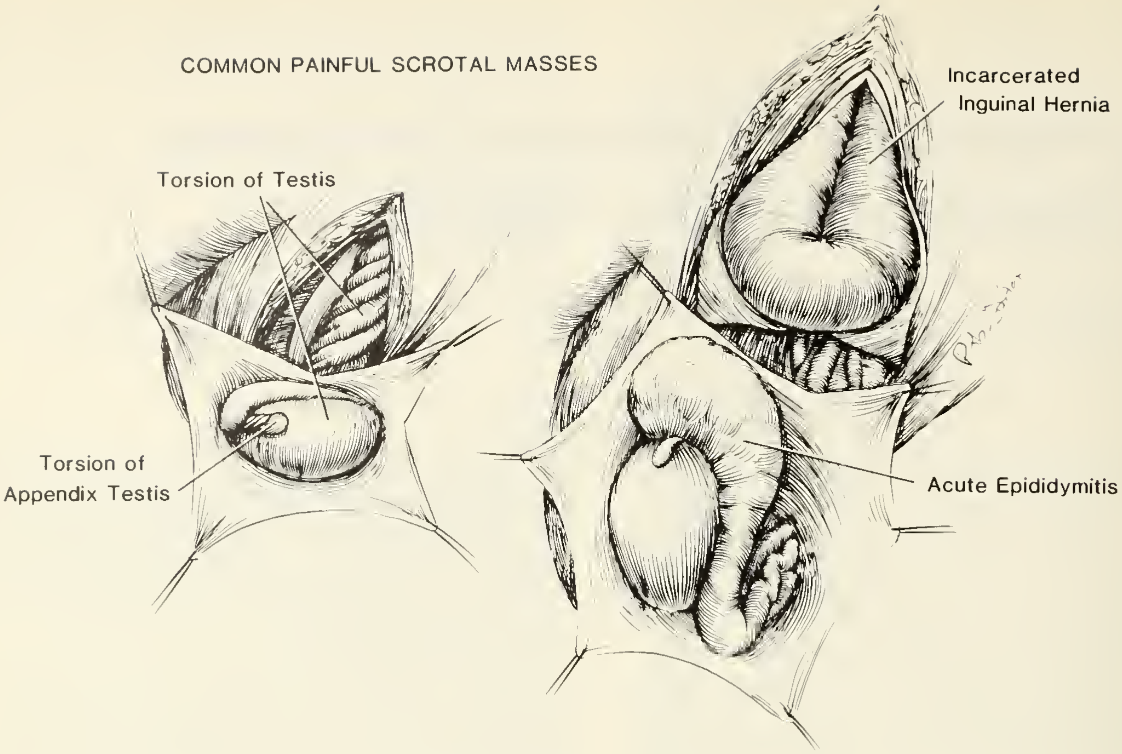
COMMON PAINFUL SCROTAL MASSES
Torsion of Testis
Torsion of Appendix Testis
Incarcerated Inguinal Hernia
Acute Epididymitis

Figure 1. *Painful Scrotal Masses*

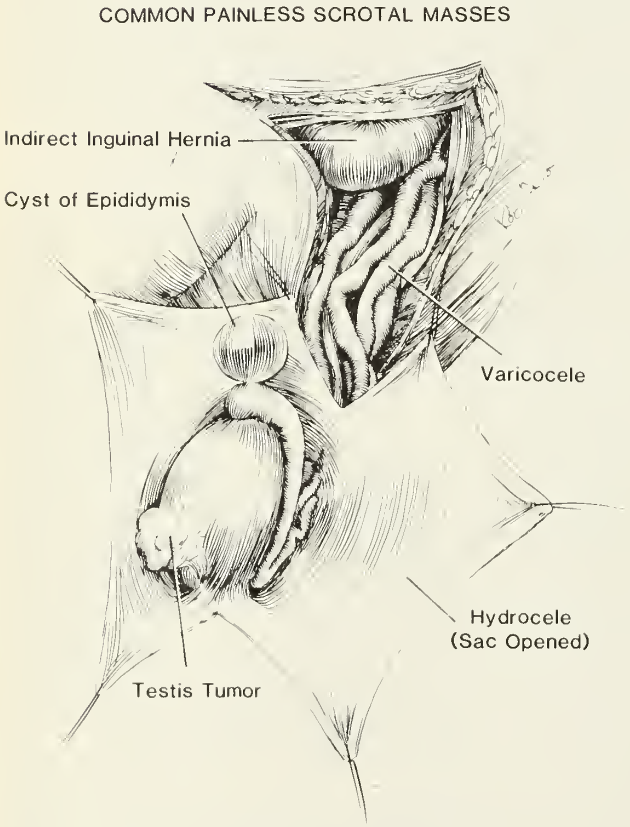

Figure 2. *Painless Scrotal Masses*

An indirect inguinal hernia is the only scrotal mass that is intermittently present. The mass may be reducible and a thumb and forefinger applied around the spermatic cord at the external ring will not confine the mass to the scrotum. Auscultation of this scrotal mass may reveal bowel sounds and the mass will not transilluminate.

Cysts of the epididymis usually involve the globus major of the epididymis (superior pole) and although they contain fluid they are often firm. If these cysts contain sperm, they are appropriately designated as spermatoceles. These scrotal masses on physical examination can easily be separated from the testicle and they will transilluminate.

Testis tumors present as a symmetrical, smooth, firm enlargement of the testicle or a firm nodular mass which arises from the testicle. On physical examination it is the only common scrotal mass which can not be separated manually from the testicle. Rarely if there has been necrosis and hemorrhage within the testicle, the testicular mass will be painful.

Self-Examination of the Testicle

Since the testicles are readily available for self-examination and testicular carcinoma is the most common solid tumor in men between the ages of 15 and 40, it would seem appropriate that the individuals at risk be instructed in self-examination of their scrotal contents.

Manual self-examination of the testicle is performed with the thumb on the anterior surface of the testicle and the remaining fingers behind. Back and forth movement of the thumb over the anterior surface of the testicle will delineate any mass protruding from the surface of the testicle. Extratesticular masses can be identified by interposition of the thumb and forefinger between the mass and the testicle proper. Any scrotal mass outside of the testicle is not a testis tumor.

Self-examination of the testicle should be initiated at the 10th grade level and re-emphasized during subsequent routine school physical examinations or on office visits for other complaints. Audiovisual presentations and models demonstrating abnormal scrotal masses would enhance this effort.[2] Clearly prior to patient education, there must be physician education. This would have to be initiated during medical school training and continued through residency programs. There has already been general public acceptance of self-examination of the female breast, and self-examination of the testicle would seem a logical step forward.

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SOCIOECONOMIC ISSUES

North Carolina Hospital Utilization — We Can Change!

William W. Fore, M.D.

• *Physicians who want fee-for-service medicine to remain an option in North Carolina are well advised to look at their hospital utilization rates.*

HOSPITAL utilization is decreasing in North Carolina. The change began before the implementation of payment by diagnosis related groups (DRGs) for Medicare patients, and the rate of decrease has increased since DRGs have been in effect. Even with our 11% decrease in hospital utilization, there is still room for improvement. The problem is that during this period of change there remains a wide range of utilization over the one hundred counties in our State. This difference between the counties with high and low rates of utilization is 136%. Is it going to be necessary for all of the negative incentives such as preadmission certification, peer review contract quotas, and prepaid medical care to be in place for the physicians in our state to lower medical costs by decreasing hospital utilization?

This journal recently reviewed the history of the 20-year progression of Federal regulation of our practices while we enjoyed the best incomes primary care physicians ever had in this country.[1] During these years the high cost of medical care was carefully studied and analyzed. Control escaped the purchasers of medical care and the medical profession. Our patients got their care when they wanted it or needed it, and on the whole got the best medical care in the world. There were no incentives for physicians or patients to decrease cost because two-thirds of the medical care bills in our State are paid by the Federal and State Governments and business corporations. The health care bill has increased by 15% to 30% a year, and in 1983 and 1984 we saw the concern over cost turned into action. The ideal situation — to have positive incentives for change — did not happen. Our behavior is being shaped by competition, denial of payment, preadmission certification, prepaid medical care, and fixed reimbursement. The majority of us practice in an honest manner and have a sincere concern for our patients. We do so in a fashion shaped by the commitment that strengthened us through the long years of school, our training, and the expectations of our patients.

There is a great deal of information on hospital utilization in North Carolina. Information on hospitalization in 1982, 1983, and 1984 is available from Blue Cross/Blue Shield.[2, 3] These figures include an over-65-year-old population of less than 2%. In 1982, North Carolina averaged 802 hospital days per 1,000 subscribers. An 11% decrease to 685 hospital days per 1,000 subscribers occurred in 1984. Approximately 25-30% of North Carolina counties are above this average figure. Health maintenance organizations have utilization rates of 300-600 days per 1,000 eligible patients.[4-6] HealthAmerica, a prepaid plan expanding rapidly in North Carolina, states that their hospital utilization is 20% below the HMO figures and 40% below all BC/BS plans.[7] Patients in the 65-year or older category are not in plans with these lowest figures nor are they the target population of HealthAmerica. An annual utilization rate of 500-600 hospital days per 1,000 patients (under 65) is not an unreasonable goal in North Carolina. Less than 20 counties have hospital utilization in this range. There is room for improvement.

Since 1979, the difference in practice patterns in our State has been recognized by the North Carolina Blue Cross/Blue Shield (BC/BS) Corporation and state agencies.[2, 3, 8, 9] There is a 136% difference in hospital utilization over our state. If we look at the extremes of hospital utilization in the counties in North Carolina with the 1983 data for admission rates, there is 125% difference in admissions and 146% difference in hospital days per 1,000 subscribers. If one then matches the county population and the physician-patient ratio in a comparison of these counties, there are still large differences: 81% and 93%, respectively. Does this wide range of hospital utilization occur in a population other than that of the North Carolina BC/BS population? It does! The medical program for the aged, blind, and disabled has a 330% difference in hospital utilization over our state. The State Center for Health Statistics has 179% difference in discharge rates between two counties of similar size. We therefore have a difference across our state of at least 100% in the way we use our hospitals for patient care. If one looks at hospital availability, county population size, and numbers of physicians, it is difficult to generalize as to why this situation exists. One is left with the conclusion that it is due to the difference in practice patterns.[2] Therefore, it is due to physician behavior. Education in the best of worlds should modify physician behavior. Does it?

The North Carolina BC/BS organization selected counties with high admission rates for respiratory diseases and found little change in admission rates after extensive education efforts in the target counties. A recent article shows that education does not change hospital utilization or de-

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crease cost.[10] Dr. Carl Lyle et al showed at 31% decrease in physician initiated charges by an intensive cost awareness program at the Charlotte Memorial Hospital.[11] They analyzed inpatient and outpatient lab charges and length of stay, and their physician group was residents in a city hospital teaching service. This study did not address cost saving by decreasing admission rate. It is difficult, with the above facts in mind and physicians' characteristics of individuality, to approach each county with the facts and expect that practice patterns will change and that the desired decrease in hospital utilization will result. I recently spoke to a county medical society about its high rate of hospital utilization. This county has two hospitals with an adequate number of physicians. The doctors had two excuses. One was, "My hospital has a lower per day cost than Duke Hospital or the Raleigh hospitals." Regardless of the daily cost a hospital saves money if unnecessary admissions do not occur. The second excuse was that their patients were being admitted by doctors in another county. The county with the highest hospital utilization has 1,257 hospital days per year per 1,000 subscribers, and sends most of its patients to an adjacent county hospital which has 818 hospital days/1000 for their residents. A recent study by BC/BS has shown that in our state 61% of our patients are hospitalized in the county in which they reside.[3] With these facts it is hard to blame higher utilization entirely on the doctors in the next county. Excuses such as these only delay the changes that need to be made.

The fee-for-service practice of medicine in North Carolina has provided a high level of care. Patients and doctors prefer a strong patient-doctor relationship. Our current system of medical care, however, with a strong doctor-patient relationship, has not controlled the rapid escalation of medical care costs. The fee-for-service system is worth saving and should not lightly be abandoned. If the State and Federal Government and the business corporations of North Carolina see that fee-for-service doctors can effectively contain costs there would be less pressure to move to prepaid health care.

Diagnosis related groups have only been in effect since October 1983, and this has certainly had an effect, but the largest decrease in hospital utilization is probably due to outpatient surgery. In Pitt County for 1983-1984, there were approximately 430 outpatient surgical procedures done each month. This is 38% of the surgery being done in Pitt County. This surgical rate alone could account for a 20% decrease in hospital admissions and thus exceed the average decrease of 11%. Fourteen counties have remarkably high hospital utilization. There are two counties that exceed the average state hospital utilization figures by 130% from all three sources in all parameters reviewed,* there are eight that exceed the 130% of the average from at least one source, and there are four additional counties that exceed the average hospitalization utilization rates by 14-44% from the State Center of Health Statistics. These counties also have two problems: a greater number of surgical procedures per unit of population and fewer procedures done in ambulatory units. Five of these 14 counties have very low outpatient rates for the 18 surgical procedures† being monitored by BC/BS. Therefore, an effective decrease in hospitalization will occur only if the practice patterns of the North Carolina surgeons in these counties change as they select the patients to have surgery and the site where the surgery is performed.

The 14 counties with high hospital utilization are geographically spread all over the state. The population of the counties varies from 8,900 to 74,100. The physician: population ratio varies from 1:8,900 to 1:685. It is impossible to say that this high hospital utilization is due to the fact that the physicians and surgeons are overloaded. There is no generalization that can be made regarding the population they serve. The high utilization practices cross all socioeconomic groups since the same information is available from BC/BS and the Medicaid program. The reason our utilization varies greatly is due to the way we as physicians practice and utilize our hospitals.

Why do anything about hospital utilization? Hospital utilization is the primary target of cost containment efforts in our state at this time. If fee-for-service physicians in North Carolina make a dramatic change in hospitalization it would show that our concern about the rising cost of medical care is sincere. Any county that lowers its utilization rate dramatically will be looked on very favorably by industry seeking future sites for plant construction. The various prepaid medical care programs are moving rapidly into North Carolina and the nation. They will not replace these fee-for-service physicians if we compete with a reduced level of hospitalization. If we do not lower our hospital utilization, then all of the programs with their negative incentives, such as the ones in place at the present time, will be extended by government, industry, and insurance companies to obtain lower medical care costs. We will be the pawns not the players in this coming game to "trim the fat" from the high costs of medical care.

How does one accomplish lower hospital utilization?

First, let's admit there is a problem. Second, let's throw away the excuses and not put it on the doctors in the next county. Third, let's analyze what we can do to change our community to provide quality outpatient care for those problems we now admit to our hospitals. Fourth, let's stop using hospitalization as a method of postponing the history, physical, and diagnostic planning for our patients to the evening hours to be performed by ourselves or our consultants.

Some specific areas to consider are:

Do you know that businesses evaluate statistics on practice patterns when choosing a community for a plant site? Counties with high hospital utilization will have trouble getting new industry.

Does your radiologist provide instruction to prepare patients for outpatient examinations?

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* Blue Cross and Blue Shield of North Carolina 1982, 1983; Pediatric hospital utilization, hospitalization for injury and poisoning, hospitalization for ill-defined illness, hospitalization for genitourinary disease and respiratory disease. Division of Medical Assistance Administrators Letter 1983; data on medical patient population. State Center for Health Statistics 1982; discharge rates per 1,000 populations.

† Myringotomy with tubes; removal of tonsils and adenoids; abdominal hernia repairs; excision of breast masses; D&C; laparoscopy; Bartholin gland surgery; therapeutic abortion; insertion of intraocular lens; arthroscopy; carpal tunnel decompression; excision of ganglion; excision of Mortons neuromas; skin grafts; cystoscopy; bronchoscopy; endoscopy; colonoscopy.

Does your Home Health Service provide hospital services such as intravenous therapy and parenteral medications?

Does your county medical society conduct a program of public education as to the necessity of doing as an outpatient many things that in the past were done in the hospital?

Are you referring your patient to a surgeon who uses an ambulatory surgical unit?

Does the ophthalmologist who sees your patient do lens surgery in an outpatient facility?

Have you identified patients with pneumonia who can be seen in the office and treated at home with close office follow-up?

Do you treat urinary tract infections without nausea and vomiting at home and get appropriate studies as an outpatient?

Do you have patient instruction sheets regarding home care already prepared for your patients?

Does a difficult diagnostic problem really need admission for lab, consultation, and x-rays?

Do you encourage a mother to stay home with her sick child rather than compete with hospital aides?

Is your local hospital developing a wellness program?

When you order diagnostic tests on a patient, do you consider cost?

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Renal Autoregulation, Drugs, and Acute Renal Failure

William B. Blythe, M.D.

• *A primer on renal autoregulation for the clinician.*

IF they recollect it at all, most physicians remember the phenomenon of autoregulation of renal blood flow and glomerular filtration rate as a rather mysterious, perhaps pedantic, principle which was solely the domain of the renal physiologist in his animal laboratory, one which was bereft of any clinical usefulness and never to be considered again after the basic-science years of medical school.

As a result of the development of certain classes of drugs in recent years, renal autoregulation has moved squarely into the clinic, and at least an awareness of it, how it can be deranged, and the serious consequences that can ensue when it is interfered with, can help keep the physician out of trouble.

Renal hemodynamic autoregulation is concerned with keeping renal blood flow and glomerular filtration rate relatively constant over a wide range of renal perfusion pressures. Changes in renal vascular resistance effected by changes in resistance in either the afferent or efferent arterioles — or both, depending upon the circumstance — keep renal blood and glomerular filtration rate from rising drastically when the renal perfusion pressure is greatly increased and, conversely, keep them from falling drastically when perfusion pressure is low.

Consider the latter state. It is of particular clinical importance. In settings of reduced renal perfusion pressure, such as might occur in salt depletion, hemorrhage, endotoxin shock, severe congestive heart failure, and certain forms of chronic renal failure, renal vasoconstrictor and vasodilator systems are activated simultaneously, and the final setting of renal resistance represents the net effect of these excitatory and inhibitory influences. Although there are numerous complex facets in the process, there are two hormones that are involved that are important in our consideration. These are angiotensin II and the renal prostaglandins. Angiotensin II produces constrictor effects and the prostaglandins antagonize these effects.

If angiotensin II production is blocked, efferent arteriolar constriction cannot be effected and glomerular filtration rate will fall and renal failure may ensue as a consequence. If, on the other hand, prostaglandin synthesis is inhibited, efferent arteriolar constriction is unable to preserve glomerular filtration rate because the fall in glomerular plasma flow that results from afferent arteriolar constriction outweighs the increase in glomerular capillary pressure mediated by the increased efferent arteriolar resistance, and acute renal failure may occur in this circumstance also.

Thus, inhibition of synthesis of either angiotensin II or the renal prostaglandins may result in acute renal failure in any clinical setting in which renal perfusion pressure is reduced.

Three classes of drugs which have been developed in recent years and for varying clinical purposes fit the bill. First came the non-steroidal anti-inflammatory drugs. These drugs are used in the treatment of all sorts of disorders. It has been estimated that over five million people are exposed to them daily, a conservative figure that does not take into account the use of aspirin. They act by inhibiting prostaglandin synthesis and, although the prevalence of acute renal failure associated with their use is relatively low, one must be alert to the possibility that it may occur in situations where renal perfusion pressure is reduced.

Next came the angiotensin converting enzyme inhibitors such as Captopril, which are used primarily in treating hypertension and occasionally congestive heart failure.

It has been shown clearly that the use of this drug in patients with fixed bilateral renal artery stenosis, a situation in which renal perfusion pressure is reduced, can lead to the development of acute renal failure.[1, 2] Here the physician should be particularly alert for this possibility in treating older patients with hypertension who may have bilateral renal artery stenosis as a consequence of arteriosclerosis.

The last class of drugs to be indicated are the calcium channel blockers. These new agents, which are now being widely used in the treatment of ischemic heart disease and hypertension, block the flux of calcium ions across various excitatory cell membranes and thereby have a potent vasodilator action.

Diamond and colleagues recently reported that nifedipine, one of the slow calcium channel blocking agents, caused acute, reversible deterioration in renal function in four patients with chronic renal insufficiency.[3]

There was no evidence in the patients of any of the usual causes of acute renal failure; thus the authors postulated that the nifedipine produced deterioration in renal function by perturbing renal autoregulation through one or both of the mechanisms under discussion. One possibility is that nifedipine, by blocking slow calcium channels, prevents

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the angiotensin II-mediated efferent arteriolar constriction. The other is that nifedipine inhibits synthesis of renal prostaglandins. Either — or both — would lead to reduction in glomerular filtration rate and acute renal failure. At present, the prevalence of this happening is not known. We have seen several cases in the past two months at the North Carolina Memorial Hospital.

The message is clear. The physician should be alert to the possibility of the development of acute renal failure in patients in any of the clinical settings that produce reduced renal perfusion pressure and who are receiving any of these drugs. Frequent plasma creatinine determinations should be made. Should a rise in the plasma creatinine concentration occur, the drug should be stopped. Renal function almost always returns to normal after cessation of the drug.

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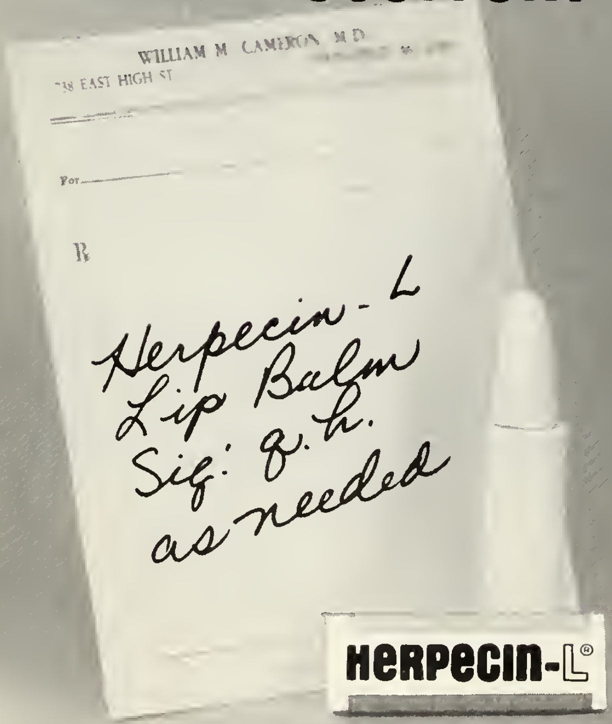

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LEARNING ABOUT WORDS

Understanding the Patient: Medical Words the Doctor May Not Know

Jeremy Sugarman and Ronald R. Butters

● *Modern medical malapropisms*

FOR centuries, the ritual and jargon of the medical profession has evoked a sense of mystery in those outside the fraternity. Writers such as Moliére have satirized the argot of the medical profession, and recent scholars have discussed the problems doctors' uses of language present for the patient.[1, 2] Serious attention has been paid to the terms used by nurses,[3, 4] the language of medicine,[5] and words used in normal hospital conversation.[6] The problems encountered as the doctor tries to understand patients has also been recognized,[7-10] but the information published to date is fragmentary, and each author seems to stress different problems inherent in doctor-patient communications. Snow, for example, gives an excellent discussion of the etiology and subtleties of a medical belief system markedly different from that of most medical practitioners, that of the folklore of black American subcultures. Such terms as *witchcraft, voodoo, hoodoo, a fix, rootwork* and *a mojo* are important medical realities for many persons.

What follows here is a synthesis of the earlier studies, expanded and brought up to date by the first author's own experience (patient interviews and discussions with resident and attending physicians at Duke University Medical Center and the Veteran's Administration Hospital, both in Durham.) We have divided patient medical talk into two categories: **Malapropism,** in which the patient confuses the pronunciation of standard medical terminology; and **Slang** and **Nonstandard Dialect** — terms that may differ regionally or socially from what the doctor may be familiar with.

A number of **malapropisms** were collected by Dr. R. Whalen and were reported in the following hypothetical case history:[10]

> The patient was a forty-year-old woman who arrived at the mercy clinic by avalanche. . . . A review of past history revealed that she had first visited the female clinic five years previously to have her service authorized. . . . Because further review of the history then revealed that she has had several athletic fits, sprangles, migrating headaches, and cascading, she [was] admitted to the hospital.

Although once understood these malapropisms seem humorous to the physician, they may initially cause considerable confusion for the doctor and embarrassment for the patient. A number of the malapropisms that Whalen reported persist some twenty years later, while others have apparently fallen from use (based on current patient interviews).*

Malapropisms

angemona [REW]	Angina pectoris
athletic fits [REW]	Epileptic seizures
avalanche [REW]	Ambulance
*bleech baby	Breech baby
*cadillacs	Cataracts
*chicken pops [REW]	Chicken pox
corollary seclusion [REW]	Coronary occlusion
*corpse suckles	Red blood corpuscles
*clogs [REW]	Clots
electrical fits [REW]	Epileptic fits
electric lights [REW]	Electrolytes
*Eucharist	Uterus
ferocious-of-the-liver [REW]	Cirrhosis of the liver (See also “roaches of the liver”)
*fireballs [REW, PCK]	Fibroids
gingeralis therapy [REW]	Digitalis therapy
gluco-in-the-vein [REW]	Intravenous glucose
gone-to-Korea [REW]	Gonorrhea
*hemogoblins	Hemoglobin
infatigo [REW]	Impetigo
mercy clinic [REW]	Emergency clinic
migrating headaches [REW]	Migraine headaches
monogram [REW]	myelogram
*Old Arthur	Arthritis, (as in “Old Arthur has me”)
*peanut butter ball	Phenobarbital
*prostrate [JFB]	Prostate
pulse [JFB]	Pus
*roaches of the liver	Cirrhosis (See also “ferocious-of-the-liver”)
*scientists	Sinuses
*service authorized [REW]	Cervix cauterized
*sick-as-hell anemia, sic-as-hell disease [REW]	Sickle cell anemia
*smiling-mighty-Jesus, spinal-moanin-Jesus [REW]	Spinal meningitis
telescoped [REW]	Fluoroscoped
terrible clombosis [REW]	Cerebral thrombosis
thrombofleabitis [REW]	Thrombophlebitis (as in

From Box 2849, Duke University Medical Center, Durham 27710.

	"No, Doc, ain't no fleas in my house")
*very-close-veins	Varicose veins
virginia [REW]	Vagina
vultures [REW]	Convulsions
*wound	Womb
wrecked fistoola [REW]	Rectal fistula
yellow jaunders [REW]	Jaundice

Another source of confused communication may result when the patient uses slang or nonstandard dialect to describe symptoms, illness, or behavior — vernacular that the non-native doctor may not be familiar with. Such terms are often consistent with medical theory, but they may also hold subtleties that correspond to the patient's conception of illness.[9] As with malapropisms, some of these terms have been described by others previously. A few of the terms listed here have apparently fallen from current usage, yet others have a surprising permanence (e.g., *high blood* 'hypertension' and *low blood* 'anemia,' described by both Snow and Whalen). The items that follow were found in folk speech primarily in the southeastern United States.

Slang and Nonstandard Dialect

agures chill [JFB]	Violent chill possibly indicating sepsis
*asthmy [REW]	Asthma
*all-nervoused up [REW]	Anxious
*bad blood [REW, LFS]	Syphilis (See also "numbers in the blood")
blind staggers [JFB]	Dizziness, lightheadedness
*blood warts [REW]	Hemorrhoids
cascading [REW]	Vomiting
*changes	Depression
corded [JFB]	Stiff, tight
deathly sick [JFB]	Nauseated
*deep study	In a depression
drawing spell [JFB]	Hyperventilation
*fall out [REW]	Syncopal episode, fainting
*falling off the roof	Menstruation
*flick	To have sexual intercourse
*getting an attitude	hostile, angry
*hark [JFB]	Cough or clear the throat
hassle (like a dog) [JFB]	Dyspnea
haven't seen anything yet [JFB]	Fear of pregnancy as well as delayed menstruation
*heart drop	Syncopal episode resulting from Stokes-Adams Syndrome
*high blood [REW, LFS]	Hypertension (But see "low blood")
*hunker [EWM]	To get into a squatting position
*in a deep study	Depression (See "changes")
*jimmies	Nervousness, anxiety
kernels [REW]	Lymph nodes
locked bowels [REW]	Constipation
loss of courage [JFB]	Loss of sexual desire or potency
*low blood [REW, LFS]	Anemia (But see "high blood")
*making water	Urination
my head rose [JFB]	Purulent otitis media
*nature	1. libido, 2. impotence, 3. bowels
*nerve aggravation	Sciatica
nervous rigor [JFB]	Anxiety attack manifested by an alternating tensing and relaxing of the muscles over the body
*numbers in the blood	Syphilis (see also "bad blood")
peart, pyert [JFB]	Lively, in good health
pieted [JFB]	Blotched
*piss hard (on)	Erection common to young men upon waking
poison blood [LFS]	Septicemia, bacteria in the blood stream
pone [JFB]	Lump or swelling, usually a harmless accumulating of fat
quickie [JFB]	Having sharp pains
regina [JFB]	Vagina
risins [REW]	Furuncles, boils
runnin' off (at) the bowels	Diarrhea
salivated [JFB]	Devastated by an illness
shortness at the breast [JFB]	Dyspnea (see also "hassle")
*stretched out	Nervous, anxious
stomach is torn up [JFB]	Diarrhea (see also "runnin' off the bowels")
stubborn [JFB]	Constipated (see also "locked bowels," "torpid liver")
strutted feet	Swollen feet
suage down [REW]	Lose weight
*sugar diabetes	Adult onset diabetes mellitus
torpid liver, liver is not kicking off just right [JFB]	Constipated (see also "stubborn"; "locked bowels")
washing out the main nerve [REW]	Pneumoencephalography

*Terms previously reported by Whalen (1961) are indicated by his initials [REW]; those reported by Snow (1974) are indicated by [LFS]; those reported by Burnham (1984) are indicated by [JFB]; by Massey [EWM]; and by Kolin [PCK]. Items actually attested in our own investigation are marked with an asterisk.

Have you run into other malapropisms and/or slang expressions in your practice? If you have, write them down and send them along to the address below, and we'll publish an update with all the new ones we receive.

Jeremy Sugarman
Box 2849 DUMC
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CAROLINA HISTORY

Conscientious Objection and Clinical Care: A History of Civilian Public Service Camp No. 61 at Duke University, 1942-1946

Louis E. Swanson and James F. Gifford, Jr., Ph.D.

- *Conscientious objectors in World War II became an integral part of the Duke Hospital workforce.*

WORLD War II produced serious shortages of clinically trained manpower in hospitals across America. While the calling-up of physicians was carefully planned, the more random drafting of attendant staff seriously curtailed the operation of many institutions. Beginning in 1942, the Selective Service began efforts to relieve these shortages by assigning units of conscientious objectors to serve as attendants in mental health facilities.[1] Conversations between Dr. Richard S. Lyman, Chairman of the Department of Neuropsychiatry at Duke, and Charles F. Boss, Executive Secretary of the Commission on World Peace of the Methodist Church, led to the establishment of Civilian Public Service Camp No. 61 at Duke in December 1942. The result was an experiment, unplanned by the organizers of the unit, in the utilization of highly educated laypersons for clinical duties and responsibilities well beyond the minimum requirements of the attendant's job. The service of the sixty-eight men who rotated through CPS No. 61 made a major contribution to keeping Duke Hospital running during the war, contributed also to a constructive national critique of health care for the mentally ill and prepared a number of these men for health-related careers. Twenty years after deactivation in 1946, appreciation of their achievement helped prepare acceptance at Duke of the design of a new answer to clinical manpower shortages, the physician's assistant.

Background

The strong peace movement in the United States during the 1930s accounted for inclusion in the Selective Service Act of 1940 of provisions for alternative service for those who were conscientiously opposed to war. Men who, for religious reasons, were opposed to all military service were classified "IV-E" and inducted into the Civilian Public Service program to perform work deemed nationally important under civilian direction. Unwritten guidelines included that the work should not be too visible to the public, should not be too easy and should not support the war effort. In meeting these objectives Selective Service officials sought and received the cooperation of church leaders through a coordinating agency called the National Service Board for Religious Objectors (NSBRO). Its task was to manage Civilian Public Service Camps under regulations drawn by the Selective Service System.[2]

The earliest camps were organized for outdoor activity under sponsorship of the Forest Service, National Park Service, General Land Office, and similar agencies. Later, special service camps were authorized under nonfederal sponsorship for work in general and mental hospitals, training schools, public health agencies and state agricultural departments. There were more requests for special service units than could be manned, so there was competition for them despite the fact that financing the units was the responsibility of the sponsoring church or institution.

CPS No. 61 at Duke was a general hospital camp. Great care was taken to insure that the unit was accepted initially at the host site: negotiations to establish CPS No. 61 eventually included Dr. Richard Lyman, Dean Wilbert C. Davison of the Medical School, representatives of Selective Service and NSBRO, officials of the Methodist Church, members of the university and hospital administrations, officers of the local American Legion post, student government leaders and hospital staff.

The first unit complement was to be twenty men, ten to serve on Meyer Ward, the psychiatry inpatient ward at Duke Hospital, and ten to serve at Highland Hospital, an affiliated psychiatric hospital in Asheville. Dr. Deryl Hart, Chairman of the Department of Surgery at Duke, then requested an additional ten men to serve as orderlies in operating rooms. Selective Service agreed and authorized CPS No. 61 on October 27, 1942. Notice of the new camp was circulated through the CPS system. Thirty men were chosen from an initial applicant pool of seventy-five men already serving at more than a dozen camps in the East and Midwest.[3]

As a group these men knew little about Duke, often confusing it with other universities. A few knew of the parapsychology experiments of Dr. J. B. Rhine; a few others recognized the name of a nationally ranked football team. One had heard that a Mr. Duke had given forty million dollars to build a university in a forest. Coming to a

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From the Medical History Program and the Department of Health Administration, Duke University Medical Center, Durham 27710.

university hospital was a major incentive, however, for a group of men who, on average, were much better educated than those who normally held attendant and orderly positions. A number of the inductees had college degrees and many others some college experience. Their personal convictions about life, which led them to refuse military service, strongly supported working in the areas of medicine and health.

Duty and Development

In general terms the mission of the unit was to staff the psychiatric call units and the operating rooms. Its first official exposure to Duke Hospital was a meeting in the traditional medical school teaching amphitheater, which was somewhat intimidating to the newcomers. Vernon Altvater, Superintendent of Duke Hospital, extended an official welcome which still is vividly remembered. The men were spread around the arena in the first row of seats. Saying he wanted to make his position perfectly clear, Altvater began by drawing a line on the floor. "When I am on this side of the line I can talk to you as individuals, whether or not I agree with the position you have taken as COs. When I am on the other side of this line I am the administrator of Duke Hospital and enforce the rules and tell you what to do. Let's not mix the two. We are glad you are here; we need your help."[4]

Thereafter the men served in three distinct groups. The Meyer Ward contingent was supervised by Dr. Lyman, who also was the unit's overall director. Dr. Robert S. Carroll supervised the ten men assigned to Highland Hospital and Dr. Max Rogers was responsible for the operating room group. R. Paul Brotsman, a member of the unit, served as assistant director responsible for liaison among Selective Service, the sponsoring Methodist Commission for World Peace, and the administration of Duke Hospital. In 1943, when Dr. Lyman entered active military service, he was replaced as unit director by Dr. R. Burke Suitt.

The work week for all groups was 48 hours, including six of instruction, plus an additional six hours of training in the evenings. Pay was $15.00 per month plus room and board. This stipend compared to the $0.10 per hour, or approximately $21.00 per month, paid to German POWs working at a mental hospital fifteen miles northeast of Durham, but the COs accepted the differential in good humor and without ill feelings.

In the operating rooms the traditional tasks of orderlies were not difficult to learn, ranging from janitorial duties to nursing care. The men prepared equipment, transferred patients to the operating suites, positioned patients for surgery (figure 1), and returned them to their rooms. They located and positioned equipment, transported instruments and supplies, mopped floors, walls and ceilings, sorted linen and laundry, and in general learned to anticipate what needed to be done without instruction. They staffed the operating rooms from 7:00 AM to 7:00 PM, earning from Margaret Pinkerton, Dean of the School of Nursing, this comment: "The operating room has had to handle more cases this year than ever before. Our subsidiary help has grown progressively poorer and more unreliable. The operating group (CPS) has worked hard and under a good many difficulties. Due to their superior intelligence, they are of greater help in placing patients in position, lifting, etc."[5]

On Meyer Ward patients were admitted for intensive treatment pointed toward recovery and release. The average stay was 30 to 40 days. The men fed, clothed, and bathed patients and participated in their recreation. They administered wet sheet packs to excited patients and nursed others through shock treatments. They took TPRs (temperature, pulse, and respiration) and charted patient behavior. Miss Pinkerton noted "splendid results in carrying out occupational therapy measures planned by the doctors. This heretofore had been impossible due to . . . inferior help."

At Highland Hospital the work situation was quite different. Therapy programs were long term. More than one-half of the employees had been at some time psychiatric pa-

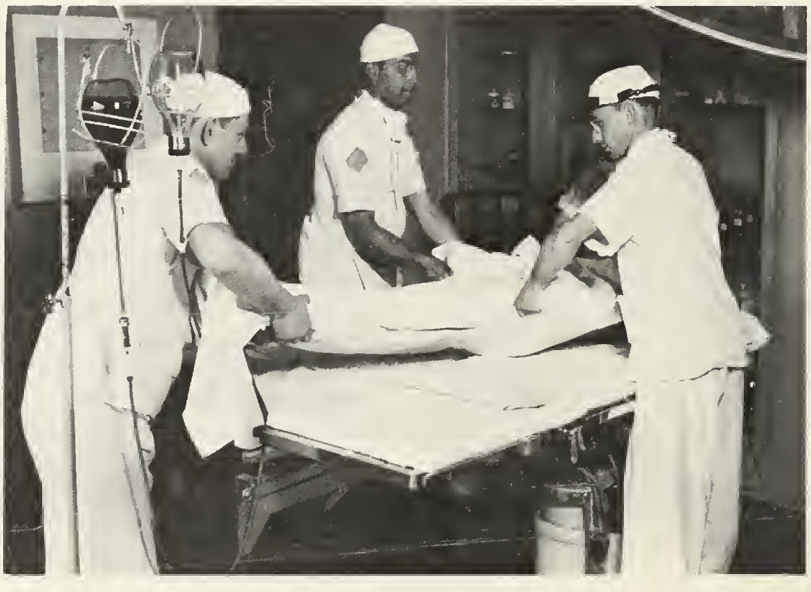

Figure 1. *Positioning a patient. Note the CO's uniform with its distinctive diamond-shaped patch on both sleeves. (Photograph courtesy of Robert Blake.)*

Figure 2. *Artist at work. (Photograph courtesy of Robert Blake.)*

tients. Some still were ill, which made life interesting for attendants. Exercise and physical exhaustion were used to maintain the physical condition and relieve the nervous tension of the patients, and both insulin shock therapy and electric shock therapy were more frequent than on Meyer Ward. Patients were at risk during these treatments and the attendants worked closely with the nursing staff to meet any emergencies. Dr. Carroll commented that the male department of the hospital might well have closed but for the coming of the CPS group. He also noted that

> Practically without exception the members of this unit who came to us directly from camp life fell into the unique routine of responsibilities and activities here with a minimum of disruptance, indeed with an unexpected maximum of efficiency. Those who came to us after some months at Duke were definitely more difficult. It would seem that to the advantages of the Highland Hospital regime they expected to find the atmosphere of University surroundings and so considerable gratuitous advice was given us, and from certain sources, criticism of conditions was apparent.

By the end of the first year the excellent performance of the inductees in their day-to-day routines and the high percentage of college graduates among them led Dr. Lyman to consider what more these men could do for his patients. ''My major interest in the unit,'' he wrote, ''has long since moved from the realm of the once needed hospital routine to that of possibilities of personal and group development, which have been started but by no means fully attained as yet.'' Encouraging the men to pursue their

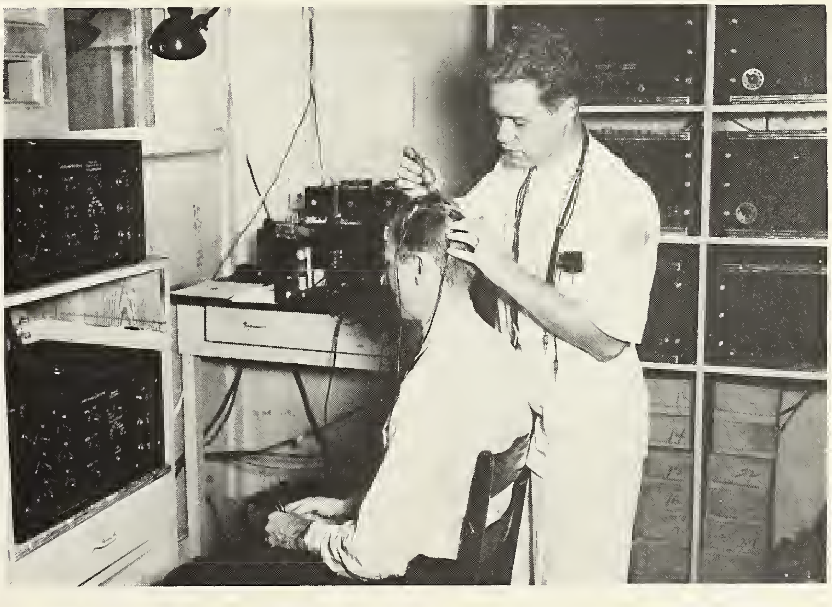

Figure 3. *Working with EEG machine. (Photograph courtesy of Robert Blake.)*

personal and professional development might save time for physicians on wards and in labs. "The point has been reached where I would enjoy being challenged to prove that we can fulfill some of these possibilities, creating values which were not even recognized to lie within the scope of this project at first."[6]

The values realized were remarkably varied. One man with previous experience in personnel work, assigned to type patients' social histories for psychiatry residents part-time, moved on to taking the histories full-time, thus freeing the residents for other work. A background in art and photography led another to work preparing charts, drawings, and photographs for research articles and exhibits and, after deactivation, to a lifetime career in medical art and illustration at Duke (figure 2). Two COs with engineering backgrounds were assigned to the EEG (electroencephalogram) lab to help keep the only EEG machine in the region running (figure 3). In the process they made several modifications of the machine that improved its performance. Other unit members maintained colonies of experimental research animals, became laboratory technicians and assistants, developed courses of physical therapy to assist patients preparing for discharge from the hospitals, and participated in research on insulin therapy, blood banking, motion sickness and recreational therapy for children. By 1943 the complement of the Duke unit was raised to 45 to accommodate transfers to full time special duty. These contributions, and the savings in trained manpower that they represented, greatly benefited Duke Hospital. As Vernon Altvater later noted, "Although your unit is small in size when it is compared to the total number of us working here, it has at times seemed to mark the dividing line between this hospital's running or being partially shut down."[7] At least five men took the M.D. degree after the war.

Diversion

Living and working conditions generally were better than in other CPS camps. Initially the men at Duke lived in log cabins first built as housing for law students. At Highland Hospital they lived in small cottages. Beginning in 1943 married couples could live off site at their own expense. There was little public reaction to the unit, and no reported or known incidents of harassment other than the loudly voiced opinions of a few individuals who resented their presence at Duke. Wives who worked in Durham felt themselves somewhat different from their coworkers but, in part because they usually chose not to discuss their husbands' work, felt little negative social pressure. Incomes were meager, but as this was true for many families during wartime, few felt victimized. Neither did the CO status impose undue pressures on the marriages, except in cases when the families of prospective wives objected to the marriages beforehand. Unit members and their families socialized with each other, and other hospital staff, during picnics in the Duke forest, bicycle and bus trips, and in softball and football games, but social contact in the larger communities was limited.

The emphasis on education that was prominent on the job continued during off-duty hours. Some evenings were spent in formal training, with lectures and demonstrations on patient problems and hospital procedures. Others were spent in "rap sessions" on topics such as the meaning of conscientious objection, the use of force in the management of patients, and issues of international concern. Still others were devoted to independent classes organized by the men, including language study in French, German, and Chinese, reconstruction in the South, and relief work motivation. At Highland Hospital, Dr. Carroll conducted classes in psychiatric theory, diagnosis and practice, noting the outstanding intellectual capacity and seriousness of purpose of the men.

Those who worked in the Meyer Ward and Highland Hospital groups, in communication with COs serving at other mental health facilities, gradually developed a sense of "responsibility to contribute to the improvement of the standards of patient care in the hospitals and later in life to contribute to the field of Mental Hygiene in one capacity or another."[8] This intention emerged out of sessions in which the men measured their work experience against their personal principles, noting conditions that should be changed and others that could be improved. Contrasting the Meyer Ward and Highland Hospital experiences led to the "gratuitous advice" and "criticism of conditions" at Highland noted by Dr. Carroll, but also to a shared conviction that "we shouldn't just point out various deficiencies and gripes but that we should do something in the line of concrete suggestions and detailed plans." Areas targeted for research included the use of force, restraint and sedatives in treatment, upgrading the role of attendant, the need to reduce public fear of mental illness, improvement of laws to safeguard patients, promotion of improved conditions of mental health in local communities and preparation for contributing to the field of mental hygiene, vocationally or avocationally, after discharge from Civilian Public Service.

Conditions at the Duke and Highland hospitals in no way resembled those discovered by COs stationed in some mental institutions,[9] where patients were poorly fed, ill housed, supervised by unqualified attendants, occasionally beaten or choked into unconsciousness, and often left for days at a time with nothing to do. As the intention of CPS inductees to improve conditions in mental health facilities became a nationwide movement, CPS No. 61 members made useful contributions because of their exposure to more enlightened standards of treatment. They collected and shared their experience through an in-house bimonthly publication called *Service*, which also presented pertinent excerpts from other publications. NSBRO published *The Reporter*, which kept the men abreast of issues and events in other camps. Nationally, CPS men organized as the Mental Hygiene Program of Civilian Public Service and published *The Attendant*, which was devoted to publishing information describing appropriate attitudes and procedures in patient care and to improving the role of attendants to the semi-professional status of psychiatric aides.[10] This journal's call for all readers to become contributors directly reflected the efforts of individual units like CPS No. 61 to improve conditions at their host sites. Some were directly involved, beginning in 1946, in the work of the National Mental Health Foundation which, with five former COs serving as the executive committee and sponsorship from such prominent public figures as Eleanor Roosevelt and Pearl Buck, documented inhumane conditions at mental health institutions and promoted higher standards of care and concern.

Conclusion

By 1946, however, the stability of the Duke unit was substantially reduced as men with longer periods of service were discharged and others worked to advance their discharge dates. There was considerable confusion at the work sites as experienced personnel were replaced with younger draftees and the more unique aspects of the CPS No. 61 experiment, the advanced personnel development projects, ended. Finally, in September 1946, the unit was deactivated.

No formal evaluation ever was made of CPS No. 61 by local hospital administrators. When the camp was deactivated the manpower shortage essentially was over at Duke as veterans returned to their jobs. But a legacy remained. In the short run, that legacy was increased expectations of job performance by attendant staff. The work of CPS No. 61 between 1942 and 1946 was the product of a unique congruence between the humanitarian convictions underlying conscientious objection and the needs of patients for competent clinical care. In the lives of these men duty, development, and diversion overlapped significantly to produce a new sense of the possible contributions of well-educated and highly motivated lay clinical staff. Although the homogeneity of the CO group was lost after the war, the possibilities remained.

Twenty years later they were realized again in vastly different circumstances. By the 1960s Duke Hospital again faced a shortage of clinically trained staff and Dr. Eugene A. Stead, Jr., Chairman of the Department of Medicine, raised the possibility of multiplying the hands of physicians in both hospitals and local communities by training bright high school graduates and ex-military corpsmen for routine clinical tasks. This represented a considerable departure from previous medical manpower policy. However, when he brought his idea before the administration of Duke Hospital, the Assistant Superintendent was a former CO who had served, by special transfer, as acting business manager of Highland Hospital in 1944 and had gone on to a career in hospital administration. His presence and recollections of the experience of CPS No. 61 made Stead's new idea seem more plausible and, although the connection is indirect, the contributions of the COs are reflected in the role of the present-day physician's assistant.

Footnotes

1. Rochefort DA. Origins of the 'third psychiatric revolution': The Community Mental Health Centers Act of 1963. J Health Pol Polit Law 1984;9:4.
2. Zahn GC. A descriptive study of the social backgrounds of conscientious objectors in Civilian Public Service during World War II. The Catholic University of America Studies in Sociology, 1953; Abstract Series 7:1-4.
3. Service, no. 1 (December 1943), 2, 14. Contains a bibliography of early articles on CPS and the Duke unit. Subsequent issues include chronicles of events at Duke and Highland hospitals.
4. Interviews with John Riebel and Robert Blake, Durham, North Carolina. Interviewed by Elon H. Clark, June 1984. Recording in Medical Center Archives, Duke University Medical Center.
5. This and the following evaluative comments are recorded in Service, no. 1 (December 1943), 6, 12. For comparison with evaluations at other institutions, see Lillian Schlissel (ed.), Conscience in America, (New York: E. P. Dutton, 1968), 234ff.
6. Service, no. 1 (December 1943), 2, 14.
7. Service, no. 1 (December 1943), 10-11; no. 2 (April 1944), 2.
8. Memorandum, undated, Louis E. Swanson Papers, Medical Center Archives, Duke University Medical Center.
9. Nina Ridenour, Mental Health in the United States: a Fifty Year History (Cambridge, Mass.: Harvard University Press, 1961), 104-7. See also Albert Deutsch, The Shame of the States (New York: Harcourt, Brace, 1948), 166ff.
10. The Attendant 2, no. 2 (February 1945), 9ff.

As of September 1, 1985, the Editor's office of the *North Carolina Medical Journal* will move from Duke Hospital to Route 1, Box 194, Bullock 27507, 919/693-4531. Dr. Stead will continue to serve as consultant to the Department of Medicine and can receive mail and messages at the usual address at Duke as well as at Bullock.

The Managing Editor's address and telephone (Box 3910, Duke University Medical Center, Durham 27710, 919/684-5728) will remain the same despite the Editor's change of address.

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Lewis gets to the heart of the matter

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PROJECT IPECAC:
An Accident Prevention Program of the Robeson County Department of Health

Thad B. Wester, M.D.

- *Thad Wester has had a distinguished career as a pediatric practitioner in Lumberton. He moved to the other side of the table to direct the Department of Health of Robeson County. Knowing that "where you sit determines what you see," I have encouraged Thad to give the rest of us his view of our activities from his new perspective. I hope that he will continue to publish in the* Journal. *E.A.S.*

THE most common health risk to children and young adults is accidents. In the preschool child, the most frequent accident-related risk is accidental ingestion of poisonous and noxious substances.

Traditionally, pediatricians and family practitioners have advised parents to keep syrup of ipecac on hand to be used to induce vomiting as early intervention. Often this advice is not heeded, leaving the family unprepared to react in an emergency situation. In such instances, over-the-phone emergency counseling from physicians and emergency room personnel who suggest the use of ipecac is useless, because ipecac is not readily at hand.

The program described, albeit fundamentally very simple, provides a solution for a community with such a problem. It also requires minimal continuous involvement, is cost effective and automatically accomplishes its objectives. In addition, it is a testimonial to the advantage of using the public health system in cooperation with community efforts to effectively accomplish a result that the private sector's one-on-one activity had been unable to obtain.

Objective

The ultimate goal of the project was to provide a one-ounce bottle of syrup of ipecac, along with instructions and educational materials, to each household in the county with a preschool child.

An estimate of the number of households can be determined by multiplying the county birthrate by five (representing the five preschool years). To this estimate we added a fudge factor of 20 percent to allow distribution to day-care facilities and family households where day care was provided by friends and members of the family.

Depending on the availability of funds, the project can be accomplished, as in Robeson County, through a crash program. In such a program, the initial distribution of ipecac and the other materials occurs over a two or three-month period.

An alternative would be a phased program that would cost less but would require four or five years to reach the desired saturation. The use of a phased program is still a critical component of the ongoing program and will be described separately.

Crash Program

We solicited assistance from the following groups: pharmacists, pediatricians and general practitioners, day-care center operators, area medical centers and clinics, the Department of Social Services, school nurses, volunteer organizations and hospital nursery and emergency room personnel. The purpose of the ipecac program and the distribution process were explained to these groups. Support for "Project Ipecac" was unanimous from each group.

Preliminary Results

The success of our program, although based on figures of limited numbers and for very short periods, still appears impressive. We have seen a reduction of 25 percent in emergency room visits for the ingestion of potentially poisonous substances during the six months immediately following the advent of "Project Ipecac," compared with the same six-month period in the previous year.

We have also realized more than a 50 percent reduction in hospitalizations. Of the four hospital admissions during the most recent six-month period, two patients were admitted for kerosene ingestion. The other two were admitted only for observation and were released within 12 hours.

(In one case, syrup of ipecac had been given appropriately and vomiting had been induced, but the attending physician felt admission for observation was worthwhile. The child was released in less than six hours.)

From the Robeson County Department of Health, Lumberton 28358.

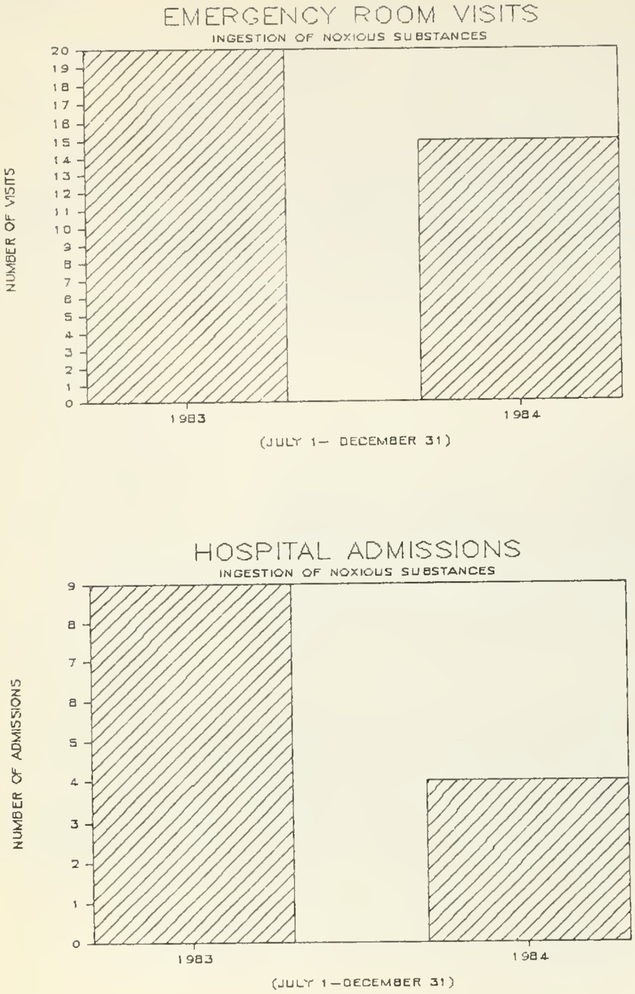

Figure 1. *Emergency room visits (top) and hospital admissions (bottom) in the years before and during the Project Ipecac crash program.*

Cost Benefit

The cost of syrup of ipecac in quantity is approximately 75 cents per one-ounce bottle. The cost of educational material is approximately 60 cents, most of which is printing costs for the booklet, "Your Child and Household Safety." The staff time to develop and implement the program came from within the health department. Other volunteer and professional time was contributed as well. The total cost of the crash program in Robeson County was 8,500 times $1.35 or $11,475.

The cost of the continuing (or phased) program will be directly related to the number of deliveries per year. In Robeson County there are approximately 1,600 deliveries each year for an annual cost of approximately $2,200.

In the year prior to the program, there were 20 hospital admissions for poison ingestions in the local hospital, two-thirds of which might have been prevented by the timely use of syrup of ipecac. The estimated dollar cost of these hospitalizations was approximately $20,000. According to preliminary data, these hospitalizations have decreased by 50 percent since the advent of the Ipecac program (figure 1). The cost of the crash program would be slightly greater than that saved in the first year of the project.

Our annual operation cost in the ensuing years is only one-fifth the cost of the crash program, yielding a 4:1 savings to cost ratio each year. The value of the other obvious benefits of preventive medicine, avoiding the stresses, handicaps and even the loss of life resulting from accidental poisonings, is incalculable.

We recommend this program to other communities if an active, efficient poison prevention program is not already in place. It is simple in concept, is cost efficient and works.

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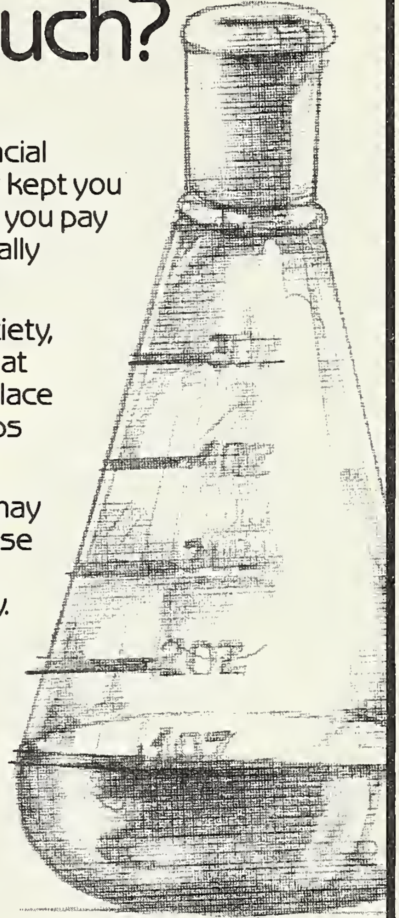

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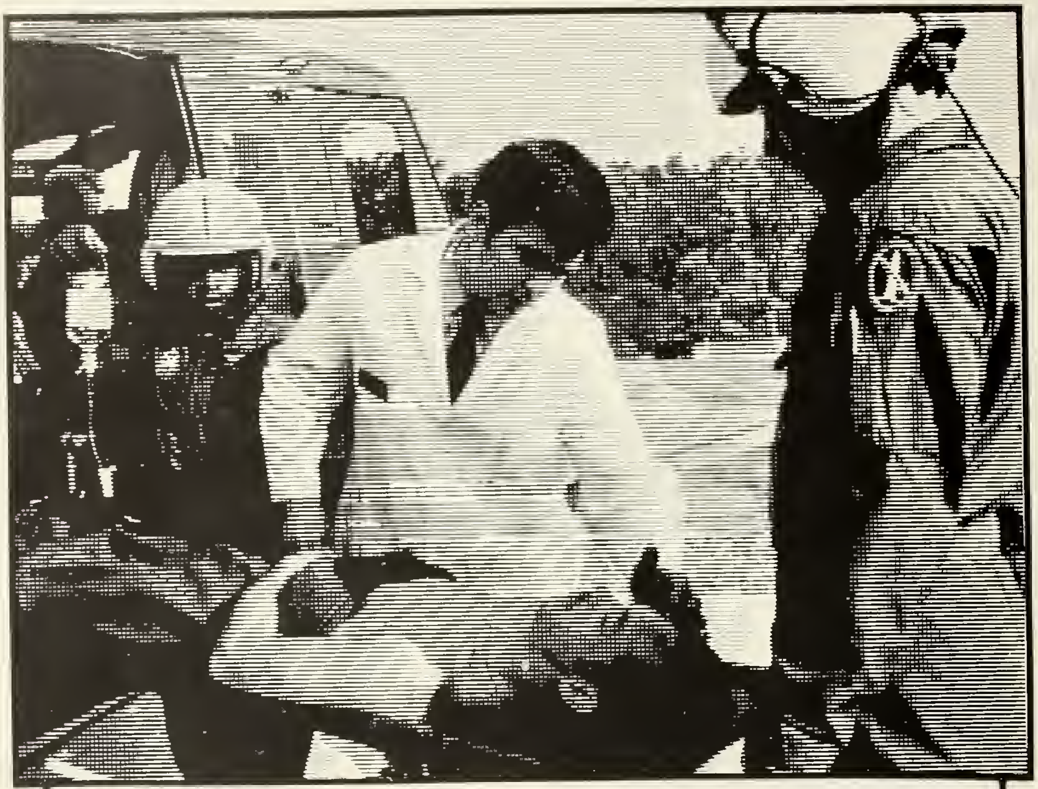

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BECAUSE SOMETIMES A 50 IS PREFERABLE.

see next page for brief summary of prescribing information

Brief Summary of Prescribing Information

NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information A Brief Summary follows

DESCRIPTION

Norlestrin Products are progestogen-estrogen combinations

INDICATIONS AND USAGE

Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles there was a pregnancy rate of 0 05 per 100 woman-years, in clinical trials with Norlestrin 2 5/50 involving 96,388 cycles there was a pregnancy rate of 0 22 per 100 woman-years

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance

CONTRAINDICATIONS

1 Thrombophlebitis or thromboembolic disorders
2 A past history of deep-vein thrombophlebitis or thromboembolic disorders
3 Cerebral vascular or coronary artery disease
4 Known or suspected carcinoma of the breast
5 Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding
7 Known or suspected pregnancy (See WARNING No 5)
8 Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

WARNINGS

> **Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.**
>
> The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1 *Thromboembolic Disorders and Other Vascular Problems* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2 0 times greater in users than nonusers, and the risk of thrombotic stroke was 4 0 to 9 5 times greater

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not Oral contraceptives, however were found to be a clear additional risk factor

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke The amount of smoking is also an important factor

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women in those with a long duration of use, and in cigarette smokers

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization

2 *Ocular Lesions* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions

3 *Carcinoma* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast cervix, vagina, and liver

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives Close clinical surveillance of users is, nevertheless, essential In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms, should be monitored with particular care

4 *Hepatic Tumors* Benign hepatic adenomas have been found to be associated with oral contraceptives Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives The relationship of these drugs to this type of malignancy is not known at this time

5 *Usage in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring* During early pregnancy, female sex hormones may seriously damage the offspring

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods If the patient has not adhered to the schedule the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptives should be withheld until pregnancy has been ruled out If pregnancy is confirmed the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy

6 *Gallbladder Disease* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives

7 *Carbohydrate and Lipid Metabolic Effects* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives

An increase in triglycerides and total phospholipids has been observed

8 *Elevated Blood Pressure* An increase in blood pressure has been reported in patients receiving oral contraceptives The prevalence in users increases with longer exposure Age is also strongly correlated with development of hypertension Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure

9 *Headache* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent or severe, requires discontinuation of oral contraceptives

10 *Bleeding Irregularities* Breakthrough bleeding spotting and amenorrhea are frequent reasons for patients discontinuing oral contraceptives In breakthrough bleeding, nonfunctional causes should be borne in mind In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy

Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives

11 *Ectopic Pregnancy* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures

12 *Breast-Feeding* Oral contraceptives may interfere with lactation Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs

PRECAUTIONS

1 A complete medical and family history should be taken prior to the initiation of oral contraceptives The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination

2 Preexisting uterine leiomyomata may increase in size

3 Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree

4 Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated

5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice If jaundice develops, the medication should be discontinued

6 Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function

7 Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency

8 Serum folate levels may be depressed

9 The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted

10 Certain endocrine and liver function tests and blood components may be affected

(a) Increased sulfobromophthalein retention (b) Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone (d) Decreased pregnanediol excretion (e) Reduced response to metyrapone test

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates phenylbutazone, phenytoin sodium, tetracycline, and ampicillin

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma, breast changes, change in weight, change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature, intolerance to contact lenses

The following adverse reactions have been reported and the association has been neither confirmed nor refuted premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication

After several months on treatment, bleeding may be reduced to a point of virtual absence, reduced flow may be a result of medication and not indicative of pregnancy

HOW SUPPLIED

Norlestrin 21 1/50 is available in compacts each containing 21 tablets Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin 21 2 5/50 is available in compacts each containing 21 tablets Each tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin Fe 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin FE 2 5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets Each pink tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin 28 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

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PD-21-JA-2563-P-1(11-84)

TOXIC ENCOUNTERS

Sisyphus on The Rocks — Monoamine Oxidase Inhibitors

Ronald B. Mack, M.D.

WHAT? You like yours with soda or 7-Up!! Shame on you — don't you remember Sisyphus? Sure you do — he was one of the most famous thieves in the history of Western Civilization but he made a few rather bad errors. One of his worst mistakes was to anger Zeus, who was the supreme god in Greek mythology; Zeus' brother, Hades (AKA Pluto), ruled the Underworld (no, not that underworld silly, the Underworld, the place where some go when they "buy the farm"!). Our hero (?) was sent to the netherworld but tricked his captors into allowing him to escape from Hell and re-enter the land of the living to avenge himself. He refused to return when asked and finally he was dragged back to the Underworld, forever, with a unique punishment: forever and ever Sisyphus was condemned to roll a huge boulder up to the top of a hill whereupon the boulder would roll back down to the bottom of the hill — this Sisyphus was to perform eternally.

Admit it, you all have had days or weeks where you feel like all you have done time after time is to push this large rock up the mountain only to have it roll right down again. Imagine, if you will, how some depressed patients must feel; pushing the rocks up the hill but getting no place. . . . In the mid 1950s a group of medications was introduced in an effort to treat depression. These were known as the monoamine oxidase inhibitors (MAOI). Why would anyone want to inhibit monoamine oxidase?

Monoamine oxidase is part of an enzyme system that breaks down certain neurotransmitters known as biogenic amines, e.g., norepinephrine, dopamine, serotonin. Many authorities believe that depression may be related to a deficiency of these amines. Monoamine oxidase inhibitors thus decrease or slow down the metabolic breakdown of these amines resulting in these chemicals being more available to the brain. (Gee, I feel better already, just by hearing all of this.) For a while the MAOIs were quite popular, but with the discovery and introduction of the tricyclic antidepressants they were used less and less. However, there has been a resurgence in the use of these agents and they are said to be efficient for the "right" patient and safe if managed carefully. One would suspect that most of us who are not psychiatrists should avoid prescribing these drugs. There are currently three MAOIs approved by the FDA for use in America: tranylcypromine (Parnate), phenelzine (Nardil) and isocarboxazid (Marplan). The latter two chemicals bind irreversibly with monoamine oxidase whereas tranylcypromine exhibits reversible findings. As you might expect, these drugs resemble epinephrine and related compounds.

The pharmacokinetics of this drug class seems to still be a mystery — in a class with the unsolved mystery of what are the ingredients that make up your offspring's choice of mate. The drugs are readily absorbed and are metabolized in the liver. In the usual therapeutic dose inhibition of monoamine oxidase may take 5-10 days although a clinical response may not appear until weeks later. Peak plasma levels in therapeutic doses are probably achieved in about 2-4 hours. Elimination half-life ($T\frac{1}{2}$) after a single therapeutic dose is about 90 minutes. Recent evidence, using the technique of measuring *platelet* monoamine oxidase levels (you mean your lab can't do them? Heavens!!), suggests that lifting of the depression occurs most favorably when 80%+ of the monoamine oxidase enzyme is inhibited. Apparently this translates into a dose of about 1 mg/kg of MAOI. There is some suggestion that very high dosage may inhibit its own biotransformation and thereby prolong the time needed to reach proper inhibition. It should be mentioned that patients vary widely in their rates of metabolism of MAOIs.

The exact toxic or lethal doses of MAOI have not been established. A minimum fatal dose is probably five to ten times the maximal daily dose although, as you might imagine, there are plenty of instances where patients have survived ingestions of this magnitude. There is a fairly long latent period between the ingestion of a toxic dose of an MAOI and symptomatology: an average period of 6.5 hours (range 1.5 to 13 hours). The toxicity from an acute overdose of this drug class is most probably due to a great potentiation of neurotransmitters because of spontaneous or drug induced release of accumulated transmitter and inhibited degradation. In other words, when you inhibit monoamine oxidase with an monoamine oxidase inhibitor the effects are on organ systems under the influence of sympathomimetic amines (e.g., norepinephrine, dopamine) and 5-HT. (Hold on just a minute — what is 5-HT? It is the abbreviated form of 5-hydroxytryptamine — AKA serotonin.) I guess what this really says is that an overdose of MAOI resembles a rather large overdose of catecholamines. Remember, these neurotransmitters will increase after an overdose only when MAO activity is inhibited by 80% or more.

Knowing these facts, it is relatively easy to figure out

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

what the clinical features of a MAOI overdose would be like. The early adverse clinical effects are those of remarkable stimulation of the nervous system. Therefore, *tachycardia* and *hypertension* are to be expected. *Hyperpyrexia* is quite common. Of course, you can expect complaints of dry mouth, nausea and vomiting. The hypertension can occur in *crisis* form with severe occipital headache radiating frontally, nuchal rigidity and photophobia. The hyperpyrexia is often quite severe and can be associated with diaphoresis and cold, clammy hands. The *hypertension* and *fever* are often accompanied by *twitching* and myoclonic fibrillation of skeletal muscles — at times leading to a *generalized rigidity* and *coma*. In many patients with this overdose the neuromuscular effects can be outstanding and it is useful to check for *hypertonicity*. The presence of *seizures* should not be a surprise either. *Dilated pupils* are de rigueur. In one recent series fasciculations, twitching, tremor or rigidity was present in 92% of patients. Severe agitation and hallucinations are part of this overdose nightmare. One rather peculiar and frightening clinical feature is the presence of a hypertensive crisis occurring contemporaneously with postural hypotension.

The clinical features of a MAOI overdose may not appear for as long as 12 hours after ingestion; signs of overdose can persist for as long as 8-10 days. Those patients whose course leads to eventual recovery begin their upward course (to health, not Heaven) by the third day and are really well by one week after overdose. When death occurs it is usually secondary to respiratory failure, circulatory failure or intracranial bleeding probably secondary to a hypertensive crisis. Very bad prognostic signs are extreme hyperpyrexia (e.g., 42°C) and irreversible hypotension. The CNS and peripheral nervous system signs you will well recognize as manifestations of excess catecholamines described by some authors as a "catecholamine storm." This clinical syndrome is also seen, as you might expect, in overdoses of cocaine, amphetamines, other psychostimulants such as phenylpropanolamine as well as a pheochromocytoma. Let me draw you an analogy — it's the sensations you felt in my old neighborhood in Chicago when someone delivered to you a fish wrapped in newspaper with a note that said "sleep with the fishes" (translation). In a recent series of reported deaths from this drug the mean time of demise was 16 hours after ingestion with a range of 8 to 24 hours. As you probably have already guessed, laboratory findings in this overdose are not really specific; if you have access to epinephrine and norepinephrine levels they probably would be elevated.

The treatment of overdose of monoamine oxidase inhibitor is not specific, in fact it's quite non-specific. Patients who are seen early and who are without symptoms should have syrup of ipecac and activated charcoal administered. Symptomatic patients should receive activated charcoal and skip the ipecac especially if it is 2 hours or so post ingestion. Many authors advise hospitalizing a patient with clinical features of MAOI overdose, even if mild, for 12-24 hours. There are so many drugs that interact adversely with MAOI that discretion is often the better part of valor here. If the patient is hypertensive enough to be dangerous you might try sodium nitroprusside or phentolamine. If hypotension seems to be the problem try IV fluids initially and if that maneuver fails use very small, titrated doses of dopamine. Seizures and excessive neuromuscular activity can be treated with a benzodiazepine such as diazepam. A beta adrenergic blocking agent has been suggested as a method to block the excessive sympathetic nervous system stimulation. The hyperthermia that can occur with this overdose is particularly worrisome and can become malignant, best treated by cooling blankets, acetaminophen or salicylate therapy. Some authors recommend the use of chlorpromazine (Thorazine) for this purpose, but don't you be tempted; don't use this drug for this purpose — uncontrolled hypotension can ensue. If the temperature won't come down and all simpler measures fail you may want to paralyze the patient with curare or succinylcholine to reduce muscle activity and to reduce shivering. Forced diuresis or hemodialysis have not been shown to favorably alter the clinical course. . . .

Excuse me for leaving so abruptly, but I must have done something wrong — Mary, the Chief's secretary, just called and said that he has sentenced me to push a box of Pampers up Pilot Mountain until next St. Swithin's Day.

Bulletin Board

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Place: Hickory
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

July 15-19
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Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: Dianne L. Willard, Bowman Gray, Winston-Salem 27103. 919/748-4505

July 16
Crisis — Then & Now
Place: Wilson
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

July 17
Diabetes/New Care Concepts
Place: Sanford
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

July 29-August 3
Diagnostic Imaging
Place: Atlantic Beach
Fee: $350
Credit: 18 hours Category I AMA
Info: Carl E. Ravin, M.D., Box 3808, Duke University Medical Center, Durham 27710. 919/681-5268

August 21
Seizure Disorders in Pediatric Practice
Place: Sanford
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

OUT OF STATE

July 19-21
5th Annual MCV Cardiology Conference
Place: Hot Springs, VA
Fee: $275
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

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Place: Isle of Palms, SC
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September 12-14
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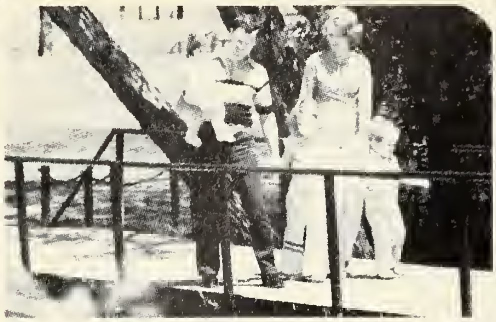

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Letters to the Editor

Bouquets for Balloons

To the Editor:

"Balloons on the CCU" by Charles Shunior is one of the best articles I have read in the *North Carolina Medical Journal* (NCMJ 1985;46:197-198). It typifies what is great about medicine — a learning, caring and loving relationship between the patient and those who provide medical care.

Congratulations.

Joseph B. McCoy, M.D.
150 Providence Road
Charlotte 28207

To the Editor:

It's nice when writing opens the door for the reader to step into another people's worlds. Specifically, I think it's helpful when we lay people are given a glimpse into the lives of medical practitioners, as in "Balloons on the CCU" in your April issue.

I thought the piece was a tremendously effective, and affecting, discussion of what it means to be a deliverer of health care — the brains and hearts that govern all that technology — and of the matter of making the most out of one's last days.

Thanks for the good article.

John B. Justice
Editor, *The Communicant*
Box 17025
Raleigh 27619

About Beard

To the Editor:

It has been some time since I have had the privilege of reading such a nice tribute as Dr. Bridges' recent one on Joe Beard (NCMJ 1985;46:303-9). It carries a strong and important message and is a landmark summary of the real background of the Duke University Medical Center.

I thoroughly enjoyed it!

David C. Sabiston, Jr., M.D.
Duke University Medical Center
Durham 27710

To the Editor:

I have just read the memorials to Dr. Joe Beard in the NCMJ. I worked with Dr. Beard for about three years in an arrangement made between him and Dr. Forbus so that I could get some research training. My career in research started there even though I did not remain in the field of virus neoplasia. He was one of the three people that I think are extraordinary in the etymologic sense of the word, here at Duke. Another one is Dr. Kempner with whom I have had some memorable exchanges only recently for the first time since I have been at Duke.

Dr. Beard did have a very warm heart once one succeeded in penetrating his gruff ways. Once I told him, exuberantly as it were, that I had just purchased a lot in Duke Forest, dreaming about owning a house and, above all, a workshop in which to build things, furniture most of all. He immediately asked me when I was going to build the house and how I was going to finance it, knowing my background. I suggested that I was not worried about that because I had two years until I had to put up the edifice. He offered me $2,000, just like that, and I started building within a month or two. I have heard over the years that he did that with many. I saw Mrs. Beard shortly after her last operation at Duke. She was in superb shape, but she told me that her life had come to an end with her husband's demise. Within a few weeks she was dead. Not exactly without precedence that, among individuals made for each other as Dotty and Joe were.

Dr. Beard was an extraordinary man. When I saw Dr. Forbus for the last time at Duke hospital, Dr. Beard asked me if I had thanked him for what he surely must have been to me. I said yes. A few months before he died, I wrote Dr. Beard a letter saying the same to him. I am lucky.

No, I don't adulate Dr. Beard, nor anybody for that matter. But I am most comfortable to have lived in the presence of people like him, whose presence is real and, almost by definition, justifies the joy of living this life.

Joachim R. Sommer, M.D.
Box 3712 DUMC
Durham 27710

Each Person Can Make a Difference

To the Editor:

To discuss abortions without mentioning overpopulation is like discussing fish without observing that fish live in water.

Abortions are not performed in operating rooms in the sky. They take place in societies which have limited capacities to raise, care for, and provide a satisfactory life for new offspring.

The Chinese do not promote abortions because they like to destroy Chinese fetuses. Instead, the Chinese are compassionate and intelligent. They realize their capacity to provide a satisfactory life for children is limited. Regardless of how intensively cultivated, their land can grow only so much food. Abortions are better than having infants and small children die of starvation and related diseases.

The United States already has evidence of severe overpopulation. We have a twin deficit of budget and trade. We live partly on borrowed resources, oil produced in other countries. We have a drug problem. We have a growing prison population, many of whom could not find a place in society. Some old people live in poverty and financial insecurity.

Fish do live in water. Abortions do take place in societies. To properly evaluate abortions, we should examine the entire picture, not just an isolated part of it.

Albert D. Warshauer, M.D.
1608 East Fifth Street
Greenville 27834

From *The Medical Journal of Australia*

Warts and all

To the Editor:

In December an anxious mother brought to me a delightful five-year-old, who had a digital wart. I offered to buy the wart from him. He was delighted when I gave him 20 cents, telling him he could keep the wart for three or four weeks, after which it would drop off, come to me and be mine. If this did not happen he was to return the 20 cents!

I thought no more about it until I had a letter three weeks later from the mother, stating that the wart had gone. Two days after this I noticed the development of a single digital wart on myself!

I write to warn your readers of yet another danger of general practice. *(PS: For sale, one digital wart, price 50 cents — yes, 50 cents — you see, I have these overheads.)*

John Troller, FRACGP
Kable Avenue,
Tamworth, NSW 2340

Pearls for Perfect Practice Under PRO

To the Editor:

Thinking about how to study a patient's problem is now (and always has been) an out-patient procedure.

Reviewing data, including slides, x-rays, op notes, path reports, and discharge summaries, is an out-patient process.

When a patient requests time in days to think things over, they must be informed that such a process should be carried on out-of-hospital.

Coming from a distance, even a great one, is not by itself an indication for hospitalization.

One shouldn't use the hospital to obtain a consultation in order to determine whether a particular invasive procedure is indicated.

If you can conclude that what you want to do for/to a patient could be accomplished in the clinic provided: that individual lived near by; you weren't real busy; you weren't going on the road; and you had time to review the studies/advise the person, then the chances are a review specialist for PRO would *deny* such an admission even when those descriptors do not obtain.

Whenever possible, a physician should mentally walk through the hospital stay of an elective admission, focusing upon inter-relationships between invasive studies, days of the week, and the anticipated next step once the outcome of such studies is known.

The telephone is not always dependable, therefore when in doubt about the need for hospitalization, see the patient in clinic/office first.

Don't turn over complete responsibility for sanctioning admissions to your secretary — review the new referral or "old" patient's clinical descriptors yourself.

Harold R. Silberman, M.D.
Duke University Medical Center
Durham 27710

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Mountain AHEC: A Bridge to the Community

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for doctors and their patients

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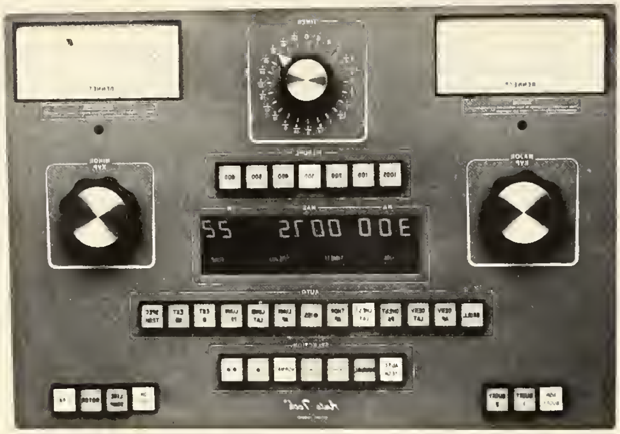

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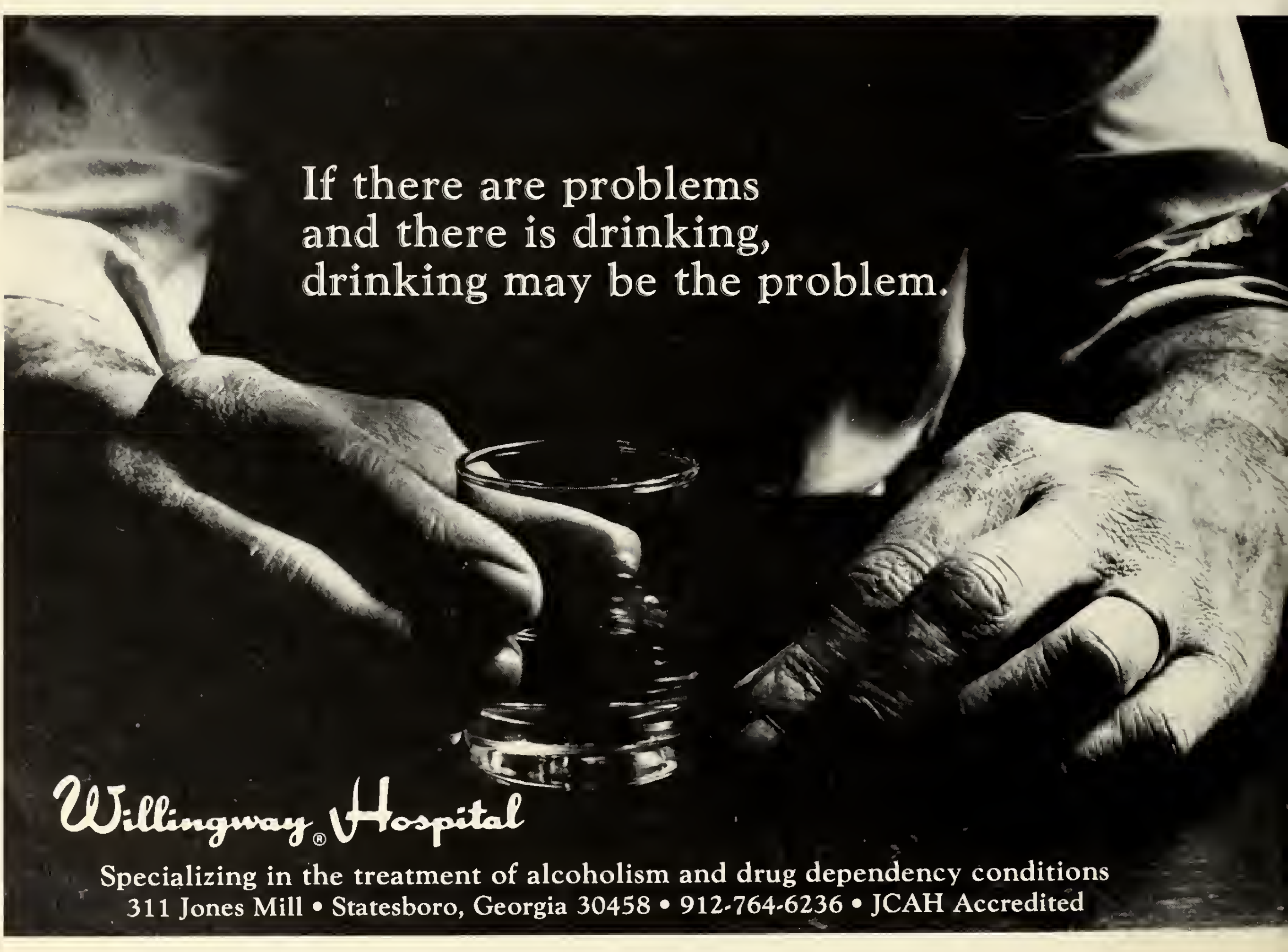

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EDITORIAL

Asheville 1985

Daniel L. Dolan, M.D.

THE medical community in Asheville is in a state of ferment. Fear and anxiety concerning physician excess, multiple prepaid health care schemes, DRGs with their eventual impact on physicians, and the opening of a new emergency room requiring coverage are high medical concerns locally. Despite the many problems, Asheville remains productive. A combined medical-surgical approach to coronary artery disease is yielding an 82% rehabilitation rate for myocardial revascularization (see review by Dr. Salisbury). A unique, low-cost, apparently safe approach to alcohol detoxification is described by Dr. Martin. An absolutely fascinating account (particularly to Asheville residents) of the early history of tuberculosis in Western North Carolina is presented in the Special Article by Dr. Stephens. I have been personally amazed to learn the background and history of places that I pass driving to work every morning. It reads like a novel and I recommend it with enthusiasm. Dr. Warren Cole, celebrated Professor Emeritus of Surgery at the University of Illinois, presents evidence that immune responses become temporarily suppressed in the perioperative period. He reviews the relationships between immunosuppression and oncogenesis.

The Mountain Area Health Education Center celebrated its tenth anniversary this past year. I have asked Drs. Bacon and Mauney to review its history and early beginnings, while it looks to its second decade of service to the region.

A local delicacy is a strong onion-like plant known as a ''ramp.'' There is an annual ramp-eating festival here each spring. Dr. Crummett reports a near disaster with amateur ramp foragers. As with mushrooms, it pays to be certain of the identification.

Dr. Gentling reports an extensive experience with a commonly used procedure: needle aspiration of breast lumps. Dr. Paschal describes results of the initial reported use of chemotherapy for a rare malignancy. These are the highlights; there is more.

We have solicited the response of six primary care physicians in the community to the new Blue Cross/Blue Shield IPA — the Personal Care Plan. Two internists, two family physicians, and two pediatricians have responded and you may read their reactions. This plan is only now beginning to be marketed in western North Carolina and will be the first prepaid plan to appear here.

Lastly, I would like to thank Dr. Stead for sharing editorship with me for this Asheville edition. I hope the readership finds something of value as well as pleasure in its contents.

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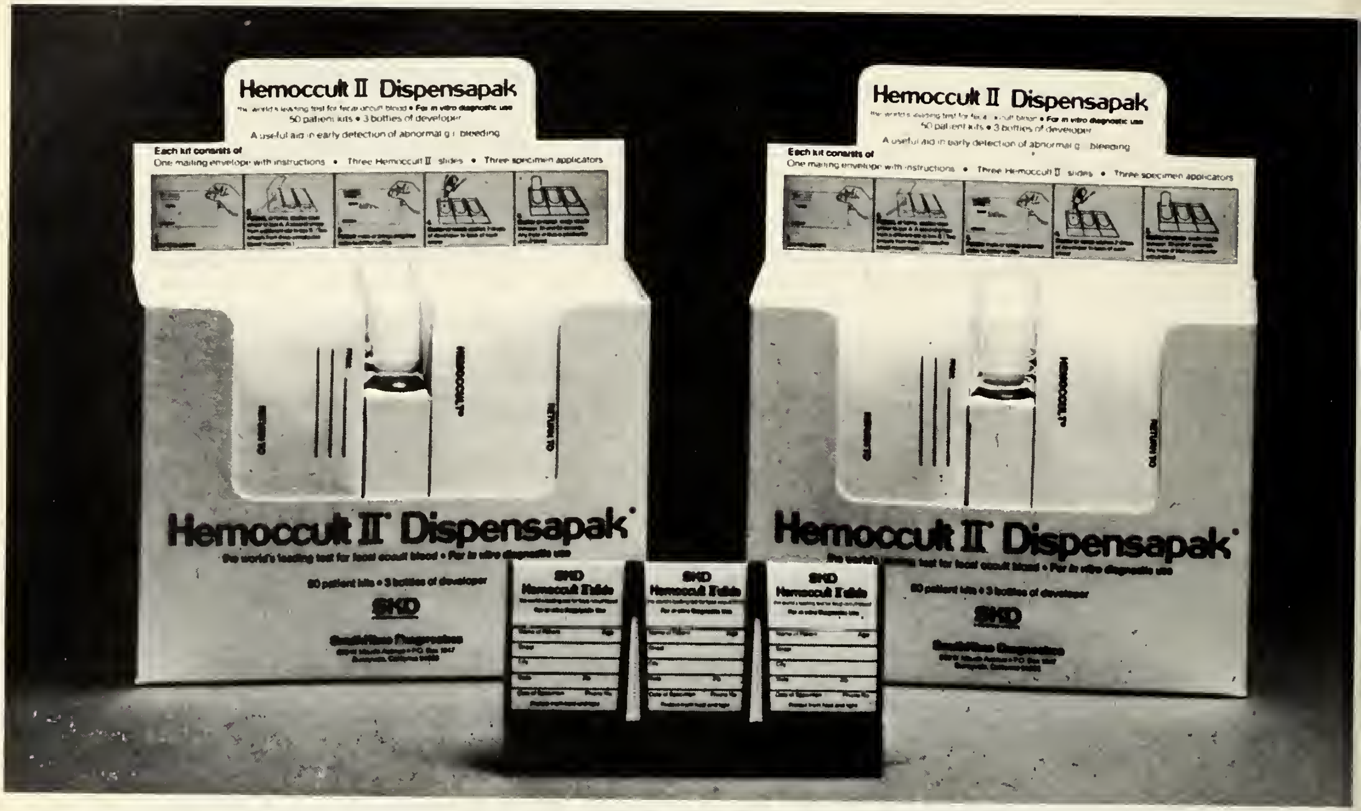
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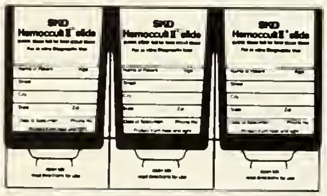

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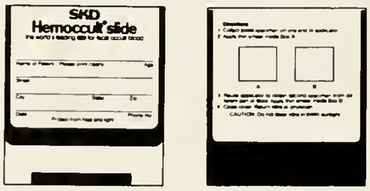

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EDITORIAL

Family Medicine at Duke: A Followup

E. Harvey Estes, Jr., M.D.

Dr. Robert Sullivan's review of the Family Medicine Program at Duke, published in the June 1985 issue of the North Carolina Medical Journal *(NCMJ 1985; 46:329-31), cited some of the environmental problems facing such a program within a tertiary medical center.*

It was written at a point in time when the demise of the Duke Family Medicine Program seemed imminent and inevitable. Fortunately (from the writer's viewpoint), circumstances changed, and on Thursday, July 11, 1985, Durham County General Hospital and Duke University Medical Center, co-sponsors of the Duke Family Medicine Program, announced that they would continue sponsorship of the program, and that recruitment of new residents for July 1986 would begin immediately.

Thus, Family Medicine will continue at Duke, at both the undergraduate and the resident level, but the events at Duke have sparked a national debate over the necessity for an educational program in Family Medicine within the increasingly complex tertiary hospitals associated with medical schools.

It is interesting to review the reasons given for initiating a Family Medicine Program at Duke in the early 1970s. These are as valid in 1985 as they were then. These reasons, as presented in 1973, are reprinted below. The economic reasons for a family medicine presence are much more urgent in 1985 than they were then. Family physicians are still in short supply, in spite of a growing surplus in other specialties. They are actively sought by HMOs, especially those emphasizing the "case manager" approach. Since HMOs are rapidly increasing in number and in patient enrollment, and since all specialty-based institutions need an ever-widening primary care base, it is urgent that they train physicians for these roles, and maintain contact with them following their training.

Those responsible for reconsideration of the role of Family Medicine at Duke are to be commended for their decision!

THERE are a great variety of reasons why Duke should have a strong, well supported Family Practice Program. These reasons can be grouped into four categories — ethical, educational, economic and political. I would like to discuss each in turn.

A. Ethical

As a medical school, we have an obligation to meet the medical needs of the people we serve.

I can present a strong case that medical schools have become autonomous to the point of becoming self-serving. The Flexnerian model of a strong biologic base for medicine has been used as a justification for creating and maintaining a gross imbalance in the quality-quantity tradeoff in medical services. When the citizens of Pinetops, Bat Cave, and even Durham complain that they cannot get medical help, our answer is that it is impractical to expect that medicine can be dispersed so widely — and that they should, instead, come to Duke, or some other center offering specialty services. This is the medical equivalent of Marie Antoinette's "Let them eat cake!"

I would not argue that we should provide a brand of quackery and call it medicine, but I do contend that a broad based generalist, who is not "turned off" by seeing common illnesses, who is willing to be concerned about convenience, access and cost, and who is willing to train and use a team of assistants is a much needed product — more so than many of the products we are now training.

The usual answer is "But that's not Duke's role! Let East Carolina do it." It is a difficult job, but that should certainly be no justification for assigning that task to a school less capable than Duke.

I do not say that we have been wrong for the past 40 years, but I do say that times have changed, and that we should change with them. We no longer have a state filled with variably trained generalists and no specialists as was the case in 1930. We have the opposite — many specialists

---

From 407 Crutchfield Street, Durham 27704.
Presentation made at the Quail Roost Conference — An annual conference for review of educational programs for medical students at Duke, May 15, 1973.

and few generalists — and we should have the courage to face the facts and change our course accordingly.

B. Educational

Duke has an obligation to provide a spectrum of models of practice for its students, all of high quality, and each treated with equal respect, both philosophically and materially.

We have not met this obligation. We do have a family practice program, which is doing *very* well, considering its environment. If you infer from this remark that the environment is not a healthy one, you are right! I hasten to add that it is not finances and/or space that stunt healthy growth — though both are indeed needed. Money alone is not enough without a change in attitude. At the present time, medical students and young doctors are often discouraged from considering family medicine as a career because of the comments made about it by respected and senior members of other branches of medicine. I am sorry to say that similar remarks are then used, without objective evidence, as a justification for lack of support for such programs. "Since so few of our students go into family medicine, we don't need to seriously consider attention to this field of training."

I accept the fact that a teaching medical center, especially a private school, should not accept a larger service obligation than it needs to support its teaching and research needs. On the other hand, we do need an example of continuous, high quality, convenient primary care so that our students can see first hand that such a thing exists! I therefore include such a model under the rubric of education rather than service.

C. Economic

A medical center is the apex of a broadly based pyramid of facilities — doctors' offices, clinics, community hospitals, area hospitals — etc. *We must continually protect, rebuild, and expand our referral base.*

For twenty or thirty years, Duke has engaged in a cannibalistic educational process. We have trained highly competent specialists and subspecialists, who have gone to the larger towns and hospitals in the state, and immediately begun to siphon off those clinical problems which once were sent to Duke. I suspect that this is a subject of concern with several clinical sectional chiefs! I propose that a healthy, expanding referral network, based in high volume, high quality family practice settings is a viable counterbalance to this trend.

Curiously, the economics of rural medicine have been used as an argument against family medicine: "Doctors just won't go to smaller towns, therefore we should only train general internists, pediatricians and surgeons who will practice in multispecialty groups." This is in many ways similar to the argument that our students don't go into family medicine, therefore we should not train them.

The internist, pediatrician, surgeon combination must have the support of a fairly sophisticated hospital, which limits choice of location. — But there is more! Doctors want to practice in groups, and groups of three seem to be the ideal size. An internist, pediatrician, surgeon combination is *not* a group, since no one can cover for anyone else. Ideally there must be three internists, three pediatricians and three surgeons.

For practical purposes, this limits such groups to cities of at least 20,000-25,000 people, since this is the population needed to support both the hospital and patient volume needs of such a group. There are only 14 towns in North Carolina which meet such specifications. There are only 36 towns of over 10,000 in North Carolina. Towns such as Hillsborough, Roxboro, Oxford, Warrenton, Pittsboro are in the below 10,000 group. My point is — we have trained people who, for economic and professional survival, *must* go to larger towns, so it is not surprising that they have not gone to rural areas. Generalist/specialist (Internal Medicine, Pediatrics, Surgery) teams must go to towns of 25,000 and up in order to survive, and subspecialists probably require a population base of 100,000 and up, but generalist (family practice) groups can thrive in towns of 5000, a suitable base for a rural ambulatory center.

The importance of this is closely related to the point previously made. If it *is* our ethical duty, as I believe it is, to fit our product to the needs of the population, then we should concern ourselves with the problem of rural medical care. This is a huge problem, nationwide in its scope, and terribly difficult to solve. I believe strongly that the provision of a cadre of doctors who *can*, if they choose, go to smaller towns and survive is an obligation which we should accept. If this is an unattractive job for a doctor, then we have an obligation to find out why, and to learn to correct this problem — new organizations, teams of individuals, new funding patterns, etc. To say that we should not concern ourselves with the *problem* is neither constructive or responsible.

D. Political

This category is the area in which all the other categories become translated into action on a public policy level and on the level of expenditure of public funds. *If we expect continued public monetary support, we must answer public needs.*

I recently attended a conference on ethical issues in medicine. The head of a major institute, in which ethical issues are under intense study, was asked who should make the final decisions regarding certain major ethical issues. His statement was that he would far rather trust 1,000 average men from Kansas to make wise decisions for the benefit of mankind than to entrust this to 100 "experts" who have studied the problems in detail.

Politics is the way in which these "average men" make their will known. In this arena, you should note the fact that several state legislatures have now required their state schools to produce family practitioners. In states in which the state school has *ignored* this call, *new* medical schools have been created, and the state dollars are now split several ways. East Carolina derives most of its support from those who do not have access to primary, generalist care. The N.C. Legislature now has a bill before it which would set aside one million dollars for the private medical schools in this state, if they are willing to establish a co-equal Department of Family Practice. This bill will probably not pass, but is should be noted as a *strong* indicator of the will of the people, as read by the legislature.

The message is clear: If we wish the support of the public, and public funds, we must listen to the message.

The message is — people want access to medical care. They want easy access, relatively inexpensive access, and continuous access. We, as a medical school, should be listening. I contend that a strong family practice program is a *necessary* part of that responsibility!

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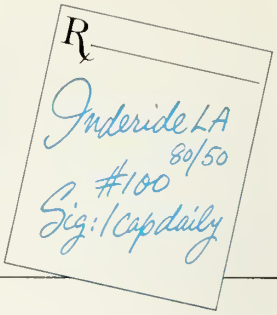
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CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated, and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure the patient should be digitalized and/or treated with diuretics, and the response observed closely, or propranolol should be discontinued (gradually if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced and the patient carefully monitored In addition, when propranolol is prescribed for angina pectoris the patients should be cautioned against interruption or cessation of therapy without the physician's advice If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure

Hydrochlorothiazide:

Thiazides should be used with caution in severe renal disease In patients with renal disease thiazides may precipitate azotemia In patients with impaired renal function, cumulative effects of the drug may develop

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma

Thiazides may add to or potentiate the action of other antihypertensive drugs Potentiation occurs with ganglionic or peripheral adrenergic-blocking drugs

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported

PRECAUTIONS

Propranolol hydrochloride (INDERAL®):

GENERAL Propranolol should be used with caution in patients with impaired hepatic or renal function Propranolol is not indicated for the treatment of hypertensive emergencies

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that propranolol may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

CLINICAL LABORATORY TESTS Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs, such as reserpine, should be closely observed if propranolol is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies, in both rats and mice employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

PREGNANCY Pregnancy Category C Propranolol has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximal recommended human dose There are no adequate and well-controlled studies in pregnant women Propranolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

NURSING MOTHERS Propranolol is excreted in human milk Caution should be exercised when propranolol is administered to a nursing mother

PEDIATRIC USE Safety and effectiveness in children have not been established

Hydrochlorothiazide:

GENERAL Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance namely Hyponatremia hypochloremic alkalosis, and hypokalemia Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids Medication such as digitalis may also influence serum electrolytes Warning signs irrespective of cause are Dryness of mouth thirst weakness, lethargy drowsiness, restlessness, muscle pains or cramps muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH

Interference with adequate oral electrolyte intake will also contribute to hypokalemia Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effect of digitalis (eg increased ventricular irritability) Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content

Any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver or renal disease) Dilutional hyponatremia may occur in edematous patients in hot weather appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening In actual salt depletion, appropriate replacement is the therapy of choice

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy

Insulin requirements in diabetic patients may be increased, decreased, or unchanged Diabetes mellitus which has been latent may become manifest during thiazide administration

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy

Thiazides may decrease serum PBI levels without signs of thyroid disturbance

Calcium excretion is decreased by thiazides Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy The common complications of hyperparathyroidism, such as renal lithiasis, bone resorption and peptic ulceration have not been seen Thiazides should be discontinued before carrying out tests for parathyroid function

DRUG INTERACTIONS Thiazide drugs may increase the responsiveness to tubocurarine

The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient Thiazides may decrease arterial responsiveness to norepinephrine This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use

PREGNANCY Pregnancy Category C Thiazides cross the placental barrier and appear in cord blood The use of thiazides in pregnancy requires that the anticipated benefit be weighed against possible hazards to the fetus These hazards include fetal or neonatal jaundice thrombocytopenia, and possibly other adverse reactions which have occurred in the adult

NURSING MOTHERS Thiazides appear in human milk If use of the drug is deemed essential the patient should stop nursing

PEDIATRIC USE Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Propranolol hydrochloride (INDERAL®):

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular Bradycardia congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System Lightheadedness, mental depression manifested by insomnia, lassitude weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place short-term memory loss emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal Nausea vomiting, epigastric distress, abdominal cramping diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory Bronchospasm

Hematologic Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

Hydrochlorothiazide:

Gastrointestinal Anorexia, gastric irritation, nausea, vomiting, cramping diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis

Central Nervous System Dizziness, vertigo, paresthesias, headache, xanthopsia

Hematologic Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia

Cardiovascular Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics)

Hypersensitivity Purpura, photosensitivity; rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress, including pneumonitis, anaphylactic reactions

Other Hyperglycemia, glycosuria hyperuricemia muscle spasm, weakness, restlessness, transient blurred vision

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn

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The Mountain Area Health Education Center: A Unique University/Community Partnership

Thomas J. Bacon, Dr.P.H. and F. Maxton Mauney, Jr., M.D.

• *A historical look at the Mountain AHEC since preparations for it began among local physicians in the early 1970s.*

THE Mountain Area Health Education Center (MAHEC) has been a vital and integral part of health professions education in western North Carolina for more than a decade. Like the other eight AHECs in North Carolina, the Mountain AHEC's major goal is improving the supply, diversity, geographic distribution, and quality of health professionals practicing in its 16-country region. This paper reviews the development of the area health education center concept, the historical advances and organizational growth of the program in North Carolina and especially in the mountain region, the major programs of the Mountain AHEC, and some of the more significant results that MAHEC has achieved in its first decade.

Historical Context

The North Carolina AHEC Program is a unique partnership between the university health sciences centers and communities throughout the state. The AHEC Program's primary mission is to improve the geographic distribution and retention of well-trained health professionals and support personnel to meet the *primary* health care needs of the people of North Carolina. Under the leadership of the University of North Carolina at Chapel Hill, the AHEC Program has evolved into a statewide educational effort that includes the other university health sciences centers in our state as well as numerous community hospitals, other university and community college institutions, technical institutes, practicing health professionals and support personnel. The AHEC Program is a collaborative effort to:

1. provide medical, dental, public health, pharmacy, allied health, and nursing students with educational opportunities throughout the state;
2. expand and enhance regional capabilities to train nursing and allied health personnel;
3. expand the regional capability to train primary care medical residents, especially in family practice;
4. increase opportunities for continuing education, in-service education, and individualized technical assistance and consultation for all health professionals;
5. provide a regional network of library and media centers that links the needs of health care providers and institutions to the most up-to-date biomedical and information resources.

The AHEC Program in North Carolina grew out of a series of community-based initiatives developed in the decade of the 60s, culminating in affiliation agreements between the UNC Chapel Hill School of Medicine and several community hospitals throughout the state. In 1970, a report by the Carnegie Commission recommended the creation of area health education centers throughout the nation. Several communities in North Carolina, including Asheville, were targeted by the Carnegie report as potential sites for an area health education center. Through a federal contract with the Bureau of Health Manpower Education of the then Department of Health, Education and Welfare, the UNC Chapel Hill School of Medicine undertook to develop a demonstration AHEC program in 1972, culminating in the establishment of three AHECs in North Carolina. In 1973 the UNC Board of Governors adopted a statewide plan for medical education, and recommended the expansion of the AHEC program to encompass the entire state. During the ensuing years, with strong and continuing support from the legislature, all nine AHECs were developed and made operational, educational facilities were constructed, and the statewide system became a major component of the university system.

The Carnegie Commission Report designating Asheville as a potential AHEC site did not go unnoticed locally as several copies of the report were circulated among hospital administrators, community leaders, regional educators, and a small number of private physicians. In the early fall of 1971, a group of five Buncombe County Medical Society members met with Dr. John Glasson, then President of the North Carolina Medical Society, to discuss ways that private physicians could support, organize, foster, and receive enhanced educational opportunities from a community-based medical education center. There was consensus that for this type of program to succeed in the Asheville region, a consortium of local and regional hospitals, as well as their medical staffs, would have to be developed.

A small steering committee met regularly during the winter of 1971 and early 1972 and rapidly expanded to include the Chief Executive Officers of Memorial Mission and St. Joseph's Hospitals, a Board of Trustee member from each hospital, and several members of the Buncombe

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From Mountain Area Health Education Center, 501 Biltmore Avenue, Asheville 28801.

County Medical Society. These persons eventually established the Health Education Commission of Western North Carolina which remained active until the Mountain Area Health Education Center was further organized.

The Health Education Commission of Western North Carolina obtained pilot funding in 1972 of approximately $36,000 through the Veterans Administration headquarters with the endorsement and close collaboration of the Oteen VA Hospital. Both Memorial Mission and St. Joseph's Hospitals contributed "in-kind" facility and staff support. With the assistance of many local governmental and educational institutions, the existing but fragmented health education programs throughout the 16-county region were inventoried and analyzed. Contemporary regional health manpower demographics were gathered and updated. A medical consultant was hired for assistance in writing and submitting several grant applications to private foundations and to the Bureau of Health Manpower Education of HEW. The federal grant application received a favorable review by the Bureau of Health Manpower Education but funding was not approved. This aggressive, tenacious, and frustrated Health Education Commission of Western North Carolina provided fertile ground indeed for nurturing the expansion to Asheville of the AHEC Program.

Even though the Health Education Commission of Western North Carolina was working diligently on the project and relying heavily on its physician members who were representing organized medicine in the community, there was a notable lack of unanimity amongst doctors in Asheville and environs concerning the AHEC concept. In mid-1972, the Buncombe County Medical Society Executive Committee formally endorsed the AHEC project and recommended that the County Society mount a collaborative effort with the two major private hospitals. At this point, Dr. Wayne Montgomery, President of the Buncombe County Medical Society, contacted the AHEC Division of the Dean's Office at UNC-CH to explore the feasibility of expanding the existing pilot state AHEC Program to Asheville. Local physicians took a strong leadership role at this point and the initial meetings were exclusively with Medical Society members at the Medical Society's express invitation.

Dr. Glenn Wilson, the first state AHEC Program Director and Dr. Eugene Mayer, Deputy Director (now Director), led the discussions in Asheville in the early part of 1972 and again in November-December of 1972. Slowly and steadily, support and understanding of the AHEC concept expanded. Unfortunately, there were no monies to expand to Asheville immediately, but in early 1973 the University of North Carolina Board of Governors adopted a statewide plan for medical education and recommended the expansion of the AHEC Program to encompass the entire state. The Asheville groundwork was in place and the two years of intensive planning paid off, for the speed with which the Mountain AHEC was organized, funded, and implemented was impressive.

In early 1973, there existed a Buncombe County Medical Society Advisory Committee, which formed the core of what would eventually become the Board of Directors of the Mountain Area Health Education Foundation, Inc. (Membership: three members of the Buncombe County Medical Society and two members each from Memorial Mission and St. Joseph's Hospitals — the Chief Administrative Officer and a Trustee from each hospital). There was also a letter of agreement with the University of North Carolina at Chapel Hill, and in the words of Henry S. M. Uhl, M.D., first director of the Mountain AHEC, there were "high hopes sustained by optimism and a vision."

The Mountain Area Health Education Center Charter Board was authorized in 1973 to recruit a Director. Dr. Henry Uhl was appointed and assumed his duties on September 1, 1973, when the Mountain AHEC offices were established and space made available at Memorial Mission Hospital.

The Mountain Area Health Education Foundation, Inc. was incorporated in February 1974, with Dr. John McLeod elected as the first Board Chairman. Operational and capital grant contracts between the Foundation and UNC-Chapel Hill were signed in July 1974. The basic design for the educational building, a unique bridge structure joining the two hospitals, was approved in June 1974. The construction plans were approved in February 1975, and construction contracts were signed in May of the same year. Recruitment of a dynamic and highly competent educational staff was begun in early 1974 and continued over the next two years as continuing medical education programs were initiated and the framework was completed for implementing a free-standing Family Practice Residency Program and Family Nurse Practitioner Program. Both of these were approved in late 1975.

While the initial thrust of the program development of necessity was centered in Asheville and Buncombe County, the *regional* hospital and medical manpower educational needs of the entire 16-county region has always been a paramount goal of the Mountain AHEC. To that end, its board of directors, its outreach programs, and its regional priorities have expanded in a stepwise fashion over the past decade. The Mountain Area Health Education Center owes much to the countless volunteers who nourished a dream and persevered in hundreds of committee sessions until the bits and pieces of this complex organization came together and amalgamated.

Since 1975 the Mountain AHEC has grown into a large and complex education institution for health professionals. The educational activities span the entire array of health care disciplines and involve undergraduate, graduate, and continuing education. With a staff of some 65 professional and support personnel and a budget in excess of three million dollars, the Mountain AHEC has become an institutional force in the health care system of the western part of the state. The programs described below remain consistent with the overall goals and structure of the North Carolina AHEC program, yet are responsive and unique to the changing health care needs of the providers and institutions in western North Carolina.

Program Activities

Family Practice Residency Program

As one of the cornerstones of the AHEC Program statewide, the training of family physicians has been a high priority of the Mountain AHEC from its inception. Founded as a department in 1975, the Family Practice Residency

Program is an excellent example of the partnership that exists between the University of North Carolina at Chapel Hill School of Medicine and the regional health care institutions in western North Carolina. Five of the full-time faculty members are tenure track professors in the Department of Family Medicine or Department of Internal Medicine at UNC-CH. At the same time, an additional twelve are part-time community-based faculty who participate in a significant way in the teaching program. In addition, nearly 100 other community-based physicians in the Asheville area contribute their time to the residency program.

Since its beginning, the Family Practice Residency Program at the Mountain AHEC has graduated 48 family physicians as of the summer of 1984. These graduates are now practicing throughout the western part of the state as well as elsewhere in the United States.

The residency program in Asheville has developed a national reputation for its innovative curriculum, which includes a strong orientation to family systems, an emerging emphasis in geriatrics, and an increasing focus on health promotion and disease prevention. Through its high quality faculty, a curriculum responsive to national and regional trends, and a commitment to place its graduates in the underserved towns of the region, the residency is now recognized as a national model of a community-based family practice training program.

Family Nurse Practitioner Program

The Family Nurse Practitioner Program was founded at the Mountain AHEC in 1975, in close collaboration with the School of Nursing at UNC-Chapel Hill. As the only diploma program remaining in the state, the Mountain AHEC's FNP Program fills a unique need for registered nurses from all educational backgrounds seeking to expand their practice as nurse practitioners.

The program continues to receive substantial funding from the Division of Nursing within the Bureau of Health Professions of the U.S. Department of Health and Human Services. Since its inception, 96 students have graduated from the program. Of these, 62 are now practicing in western North Carolina in a variety of settings, including rural free-standing clinics, health departments, private medical practices, hospitals, and other sites. Increasing interest is being shown by industry in employing nurse practitioners to manage and staff occupational health and health promotion programs at industrial sites.

The Nurse Practitioner Program at the Mountain AHEC has a strong orientation to both behavioral sciences and geriatrics. The curriculum involves eight months of didactic training at the AHEC, followed by four months of a structured preceptorship in a practice setting.

Student Support

One of the major elements of an AHEC as envisioned by the Carnegie Commission was the rotation of students from university health sciences centers into regional AHEC centers. As a priority of the North Carolina AHEC Program from its inception, the Mountain AHEC has seen a steady growth over the years in the number of students seeking clinical placements in western North Carolina. Approximately 250 students spend a portion of their clinical time on rotation to one of a number of clinical facilities in the mountain region each year.

An excellent example of a high-quality student experience involves the rotation of senior pharmacy students from the School of Pharmacy at UNC Chapel Hill. Each year, ten to fourteen senior pharmacy students spend an entire semester working in the Mountain AHEC region. These students are placed in hospital and community pharmacies, and are closely supervised by the AHEC Pharmacy faculty member housed at the Mountain AHEC. Students come together each week for seminars, and also participate in structured learning experiences in the clinical setting. Services provided to students on rotation to the mountain region include housing, library and media services, other logistical support such as travel, and assistance in exploring opportunities for future practice.

Information and Media Services

A major service provided to all health sciences students and practicing health professionals in the region are library and audiovisual services under the auspices of the Department of Information and Media Services at the Mountain AHEC. The library has a collection of some twenty-thousand volumes and offers a comprehensive array of information services including reference, on-line computerized bibliographic searching, inter-library loan, consultation and technical assistance, and audiovisual production. The total number of services provided to the region from the AHEC library in 1983/84 was approximately 38,000. These services were provided not only to students and practitioners in the Asheville area, but reached health care providers in all 16 counties served by the Mountain AHEC. As a matter of fact, 45% of the services were provided to practitioners in counties other than Buncombe.

Continuing Education

Another major educational priority of the Mountain AHEC is continuing education for all practicing health professionals in the region. Organized primarily around the major health care disciplines, the Mountain AHEC offers a comprehensive array of continuing education programs from one-hour lectures to courses of a month or more in length. Approximately 350 continuing education programs are put on each year, approximately half in Asheville and half throughout the other 15 counties in the region. This enables health practitioners to have access to high quality continuing education without having to incur the expense of travel to a university health science center or a major metropolitan area. Faculty from the university health science centers as well as other constituent universities and two-year colleges actively teach in these programs. Regional and national speakers are also invited to participate on a regular basis. Survey data and anecdotal evidence suggest that the availability of such a level of continuing education has had a major impact on reducing professional isolation among health professionals in the mountain region.

Consultation and Technical Assistance

As part of the overall goal of improving the practice environment for all health professionals in the region, the faculty and staff of the Mountain AHEC provide consultation and technical assistance upon request. These services provide many individual physicians as well as health care agencies with access to the professional resources of the Mountain AHEC for solving problems relating to personnel, financial management, human resource development, and a host of clinically-related issues. The consultation is designed to augment the formal continuing education programs provided throughout the region.

The education programs described above are intended both to stand alone as services offered by the AHEC, and also to serve as an integrated and comprehensive approach to improving the educational environment for health professionals in western North Carolina. There are a number of examples of the way one AHEC program relates to another. Many of the graduates of the Family Practice Residency Program regularly contribute time teaching and precepting current residents. They are also often the individuals taking the lead in their respective counties in organizing active continuing education programs in collaboration with the staff of the Mountain AHEC. In addition, their utilization of the resources available through the library and media center further strengthen the practice environment in the small towns in the region.

Program Impact

The Mountain AHEC has had a major impact on the availability of highly trained health professionals in western North Carolina. For example, of the 48 graduates of the Family Practice Residency Program since its inception, 40 (83%) have stayed in North Carolina to practice and 75% have remained in the 16 western counties of the MAHEC region (table 1). This rate of retention exceeds that of all other programs in North Carolina, and may be unsurpassed in the entire U.S.

The intent of the AHEC-based residency programs was to place primary care physicians in the small towns in the regions that have heretofore been underserved. Table 2 demonstrates the success of the Mountain AHEC's residency program in this regard. Again, of the 48 graduates through 1984, 27 (56%) have settled in towns with a population of less than 5,000, and an additional 19% have established practices in towns of under 15,000 population. Thus, three-fourths of the graduates are practicing in towns of a size that historically has had difficulty in attracting and retaining primary care physicians. In addition, of the 36 graduates who have settled in towns of under 15,000 population, only one has not remained there permanently as of March 1985.

Table 1

Mountain AHEC Family Practice Residency Program: Geographic Location of Graduates

Location of graduates	Number	Percent
Buncombe County	12	25
Other counties in Mountain AHEC	24	50
Other counties in North Carolina	4	8
Outside North Carolina	8	17
Total	48	100

Table 2

Mountain AHEC Family Practice Residency Program: Size of Community of Graduates

Size of Community	Number of graduates	Percent
< 5,000 population	27	56
5,000 - 15,000 population	9	19
15,000 - 50,000 population	4	8
> 50,000 population	8	17
Total	48	100

In 1975, there was approximately one primary care physician for every 2,000 residents in the mountain region. At the end of 1984, the ratio was approximately 1:1500 population. Although a variety of factors have contributed to the improved availability of primary care physicians, the AHEC residency program has had a significantly favorable impact on this ratio.

The second major program to address shortages of primary care providers in rural areas is the Family Nurse Practitioner Program. Since it was established in 1975, MAHEC's FNP program has graduated 96 students. The data presented in table 3 show that nearly one-half of the FNP graduates are now located in the 16 counties served by the Mountain AHEC and an additional 16% are in other counties in western North Carolina. Although not shown in the table, a substantial portion of the graduates have settled in very small towns or rural communities that either had no physician or were clearly medically underserved.

As described above, the Mountain AHEC sponsors over 300 continuing education programs per year in the region, and targets these programs to all health professionals. Table 4 demonstrates the growth in the number of programs over the past four years, and indicates the balance of programming between Buncombe County and the other counties in the region.

Attendance at continuing education programs has risen steadily over the years as well. Although physicians' attendance in continuing education continues to far exceed that for other disciplines, its absolute size and percentage of the total has declined slightly in the past three years (table 5). Attendance by nurses has increased steadily during the

Table 3

Mountain AHEC:
Location of Graduates of the Family Nurse Practitioner Program: 1975-1984

Location	Number	Percent
Mountain AHEC region	47	49
Other western N.C. counties	15	16
Other North Carolina counties	20	21
Out-of-state	14	14
Total	96	100

Table 4

Mountain AHEC Continuing Education Programs by County Group

County	Fiscal year 1980-81	1981-82	1982-83	1983-84	Total
Buncombe	169 (57.5%)	169 (56.0%)	182 (58.1%)	196 (55.8%)	716 (56.8%)
Other Mountain AHEC counties	125 (42.5%)	132 (43.7%)	128 (40.9%)	152 (43.3%)	537 (42.6%)
Other		1 (0.3%)	3 (1.0%)	3 (0.9%)	7 (0.6%)
Total programs	294	302	313	351	1260

Table 5

Mountain AHEC Continuing Education Programs: Attendance by Discipline

	Discipline							
Fiscal year	Allied Health	Dentistry	Medicine	Nursing	Pharmacy	Public Health	Other	Total
1980-81	1390	268	4103	1513	329	383	186	8172
1981-82	1574	335	4083	1302	334	304	109	8041
1982-83	1626	689	4472	2085	323	458	104	9757
1983-84	1823	370	3879	2184	218	675	84	9233
Total	6413	1662	16537	7084	1204	1820	483	35203

same period, such that nearly ¼ of the total attendance at continuing education programs sponsored by the Mountain AHEC is by nurses.

Library and media services are a major part of the overall educational program of the Mountain AHEC. The data in figure 1 illustrate the growth in overall services through the Mountain AHEC Information and Media Services Department. The graph also shows that the increase in utilization has occurred both in Buncombe County and throughout the rest of the region, demonstrating the increased perception that the Mountain AHEC library is a regional resource, serving the health care providers and institutions throughout the entire sixteen western counties.

Conclusion

Since 1974 the Mountain AHEC has grown into a large, complex education institution for all health sciences students and professionals. Its educational activities span the entire array of health care disciplines and its programs have had a significant impact on improving the quality and availability of health care to the citizens of western North Carolina. Along with its sister institutions in the AHEC System, and the constituent campuses of the university system, the Mountain AHEC will continue to respond to the health manpower needs of its region, adapting programs as necessary to the changing health care environment.

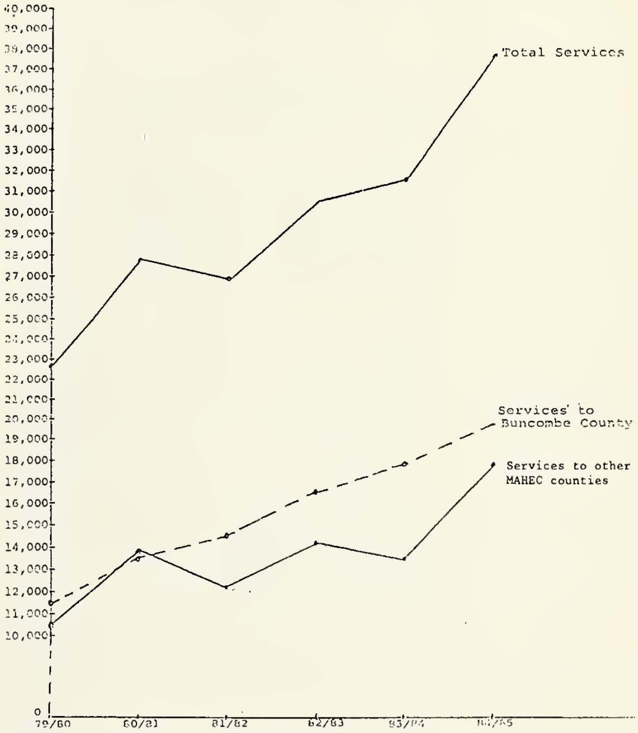

Figure 1. *Mountain AHEC information and media services. Total services delivered 1979-1985, by region and Buncombe County. Total services include reference services, interlibrary loans, circulation, audiovisual production and audiovisual users.*

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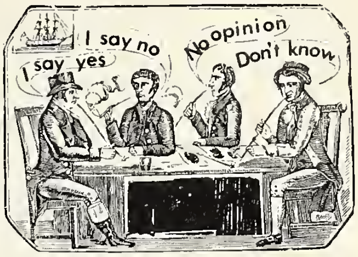

edited by Daniel L. Dolan, M.D.

The editor has queried physicians in several disciplines who practice under the rubric "Primary Care" as to how they view the effects on their practices of the new Blue Cross/Blue Shield individual practice association titled the Personal Care Plan. In brief summary, a primary care physician signs a one-year contract which can be terminated with 30-days notice from year to year. The physician agrees to accept up to 300 patients over a three-year period and be listed as a participating physician in the directory of the plan which is sold to subscribers. He must maintain hospital privileges in at least one hospital participating in the plan. He agrees to provide a four page list of services free to all subscribers in exchange for a monthly payment per patient made to him by the plan varying between $5.59 to $27.00 depending on five categories of age and sex. For an additional three pages of services, he will be compensated between $.16 to $1.58 per patient per month. Additionally, the plan credits a second monthly payment to a central Institution and Referral Fund between $25.29 to $55.53 per patient to cover hospitalization and consultants' fees. If at the end of one year, the cash flow in the Institutional and Referral Fund is positive, the physician retains 100% of his prepaid stipend plus 50% of his surplus. If the cash flow is negative, he receives only 80% of his stipend. In no instance does he lose more since larger deficits are guaranteed by the plan. Should he be unable to personally provide all of the services on the list, he must obtain these services from a consultant, but paying from his first fund. He maintains the freedom to continue other segments of his practice as he chooses. He must provide 24 hour per day, seven day per week coverage.

The question to the participants in this Physician's Forum was, ***What do you think of Blue Cross/Blue Shield's Personal Care Plan?***

From Dr. Ellen Boyd, a pediatrician in Asheville

The Personal Care Plan presented by Blue Cross/Blue Shield has the advantage over other HMO type health plans whereby consumers can choose their physician and maintain an interpersonal relationship with continuous follow-up by this designated physician. It is anticipated that by having routine scheduled check-ups, education and preventive care can be taught with early screening of developing problems for the pediatric population. Under a pre-paid plan, parents will bring their children in for acute care and hopefully problems can be managed on an out-patient basis before hospitalization is required.

The Personal Care Plan may benefit a new physician in an area by helping this physician get referrals and establish a practice. With this plan, the pediatrician needs reassurance that financially his/her practice will not be hindered and will continue to have a positive growing balance. Although emphasis is given to the fact that paper work from processing claims, billing and collections will be minimized, it is a concern that the paper work completion of encounter forms from patient visits may require more time and expense of the office personnel.

Pediatric offices presently place an additional charge for after hours visits. This encourages patients to bring their children in during regular office hours. Under the prepaid plan there is the guarantee of the standard twenty-four hour seven days per week availability of covered services to participants at no additional costs. A concern is that this may increase the demand for after hours visits and that financial incentive to come during regular office hours will be lost.

One major advantage of the Personal Care Plan is that it assures coordination and continuity of care of the participants by their personal physician. This physician is responsible for managing their health care and must authorize all referrals to specialists and preauthorize all elective inpatient and outpatient hospital admissions scheduled by medical specialists. This plan will encourage more coordination of care between the participant and all medical personnel involved with the personal care physician managing this care.

The establishment of HMOs, industrial health care plans, and personal care plans as presented by Blue Cross/Blue Shield are proclaimed as the medical care system of the future. With the evaluation of health care expenses, the ideal restraint to escalating costs would be practicing preventive care. Still, mediocrity of medical care must be guarded against. Physicians need financial incentives and there is nothing wrong with competition in the medical arena. Competition serves as an advantage to the medically served population. Pediatricians are recognized as having one of the lowest incomes among physicians. It would be encouraging to see more equality of financial compensation for services rendered, and more compensation given for the "thinking" primary care physicians. If health care plans were to distribute the health care dollars more across the board for physicians, this would be an incentive to bring more physicians into the primary care profession where the medical need is greatest. Financial incentives should be placed among the primary care profession and it is hoped that prepaid health care plans will reflect this need. The payoff in preventive primary health care would be an overall reduction in health care expenses.

From Dr. Robert H. Fabrey, II, a family practitioner in Weaverville

At the present I do not participate in the Blue Cross/Blue Shield Personal Care Plan, because it is not offered in the Asheville Area. However, when it becomes available, my associates and I expect to participate. I am a family physician in a three man group.

I became a family physician in part because I perceive some efficiencies in the way I deliver medical care. Continuity of care is one of the tenets of family practice. Preventive medicine as manifested by risk factor control and screening for illness is an important part of our present practice. We do it because we feel it is cost effective in terms of dollars and personal suffering.

At the present time most health care insurance does not provide financial incentives for health screening. The present system encourages care of higher cost acute illness and does not reward the low cost-high touch aspects of care. The Personal Care Plan appears to address this issue, by providing funds for what now might be uncovered services. This will change my practice only in that services I already provide patients will now be reimbursed by their carrier.

I suspect that the Personal Care Plan will change my relationship with my consultants. It will force me to be more cost conscious for equal services. I expect there will be difficulties when a patient desires a consult or "second opinion" outside our office, when I can see no justification for it. I think that these are all solvable problems, but may change my practice style.

From Dr. Harold D. Schutte, a pediatrician in Asheville

Given the present climate of escalating health care costs resulting in increased interest in cost containment by insurance companies and government, the primary care physician must take note of the trends that will affect his practice over the next decade. He must also deal with a physician surplus and a shrinking patient population at the same time that he copes with an uncertain economy. It is obvious that he must have an anchor for economic and professional survival.

The introduction of North Carolina Blue Cross/Blue Shield's Personal Care Plan has significant appeal. On the surface, at least, it seems to work within the framework of the present health care delivery system. It accomplishes this by a prepaid plan for cost containment and the utilization of primary care physicians already in private practice. The plan also has provisions for early detection of disease and preventive medicine education which ideally should reduce health care costs and benefit the patient as well.

As a pediatrician in private practice I would like to have options other than one single plan to choose from in order to be able to choose the one most compatible with my style of practice. The Personal Care Plan, while stressing physician involvement in peer review, does not mention the role of the primary care physician on the governing board of its plan. This type of relationship would ensure that a specialty like pediatrics would be given adequate emphasis. In my view if involvement at the board level is not an integral part of the plan it could well appropriate a large portion of its funds and emphasis to surgical procedures, with a small amount for cognitive activities. As such, the primary care physician again would end up on the low end of the financial totem pole. It is somewhat reassuring to know that in its formative stages the plan had significant physician input. The plan's track record for accomplishing its ideal goals of ensuring quality care while reducing health costs and fairly compensating participating physicians will have to await the verdict of time.

From Dr. Lewis C. Sommerville, a general practitioner in Asheville

If I did not participate in such a plan, I am sure that there would be a certain number of my patients from industry enrolling in such a plan, and I cannot, at this time, tell specifically what percentage of patients I am talking about. However, because this would occur, I would probably feel somewhat coerced into co-operating or participating in a plan if it were very widely used in our area.

What would be the effect on my practice if I did not participate? I have looked, somewhat superficially of course, at the cost. And I have looked at the total cost of caring for patients in my office over the last year. The impression I have gotten is that the "healthier" patients, that is those in the work force who would be apt to be covered by such a plan, actually take less cost for their care during the year, and this select group then would be covered by an IPA. The other type of patients — older patients, those who take more care and have a higher cost per year — would probably not be covered by an IPA because they are not involved in industry, etc. It is my impression that 80% of the capitation fee does not quite cover the charges that I am making at the present time. This would, of course, be a deterrent to my entering into this kind of plan.

The final thing, and this would seem to be the most important, is that with a capitation fee (if I read the plan correctly) I would be required to pay consultants, lab and x-ray fees, etc., and this would tend to cut down on referrals or workups that could not be accomplished in one's own office. This, then, would tend to mitigate against the optimum care of the patient. I think, in the long run, this would tend to reduce the quality of care to a certain extent.

From Dr. Virgil Thrash, an internist in Asheville

General internal medicine is a discipline unique to the practice of medicine. The internist utilizes his diagnostic and therapeutic knowledge gained in his three to four years of residency in the multi-system dilemmas encountered in his daily office and hospital practice. These same skills are likewise invaluable in providing daily preventive and remedial primary care to the patients in his practice. Adequate time allowed for each complete physical, office visit, and hospital consultation is an absolute necessity in accomplishing these goals. An average day for any of the four general internists in our Asheville practice consists of usually twelve to fourteen office visits, each fully fifteen minutes, and four complete physicals, each one hour. Our patients are scheduled from 9 AM to 5 PM, and our hospital practice is managed pre and post office hours.

The well-trained internist cares for his patients with minimal consultative assistance from various subspecialists. With the assistance of the usual office laboratory, x-ray, and electrocardiographic equipment such care can be given both conveniently and economically. The same attempt for complete comprehensive care is also given to the patient requiring hospitalization.

Blue Cross/Blue Shield of North Carolina suggests that the answer for providing preventive, complete, economical primary care should be directed at the primary care physician. These physicians are to be saddled with the responsibility of providing or acquiring the cheapest care possible for their patients. They are to be rewarded with year-end bonuses depending on how adept they are at performing fewer diagnostic tests, admitting fewer patients to the hospital and utilizing the least expensive consultants, both medical and surgical. The comprehensive physical examination would become non-existent. The fifteen minute office visit, in which not only is the chief complaint addressed but also a brief update of the patient's problem list is made, succumbs to the hurried three to five minute encounter in which an honest effort is made to diagnose a chief complaint. Regardless of good intentions, the office visit would become thus shortened in order to accommodate more HMO participants in a financially embarrassed practice already struggling to pay a fifty percent overhead.

The increasing cost of medical care is evident. Industry is understandably attempting to place a lid on these spiraling costs, and at the same time to provide good medical care for its employees. The correct answer to this dilemma is not to force the primary care physician into a position of being "hatchet-man" for the skyrocketing costs of consultative fees and procedures, surgical fees, and hospitalization expenses. Instead, the insurance providers and industry should attack the source of the problem themselves. Evaluations should be made and maximal allowable fees established for the various surgical, medical and radiographic procedures. "Unreasonable fees" should not be paid even when performed during a hospital stay covered by major medical. Patients should be encouraged to seek inquiry concerning excessively high medical fees. Perpetual "high fee" offenders should be excluded from insurance reimbursement. Efforts to encourage and enforce more expeditious use of hospital beds should continue.

The general internist, recently having received much of the impact of the newest Medicare reimbursement plan, needs no part of a program designed to destroy his comprehensive care of patients. Industry does, however, desperately need our participation in providing an innovative, alternative answer to this major problem of increasing medical costs.

From Dr. Robert Wells, an internist in Asheville

These remarks will be addressed primarily to the Blue Cross/Blue Shield Personal Care Plan and how it would affect my practice of medicine. However, to a certain extent they apply to the HMO concept as a whole. There are certain advantages that any primary care physician would find by participating in the Blue Cross/Blue Shield Personal Care Plan. I think some of these advantages are very attractive, especially to the physician who is just entering practice. With any HMO there would be a guaranteed income. A primary care physician would be paid a capitation or fixed dollar amount per month for each patient in his assigned group of patients. This would provide a very stable guranteed source of income. It would also free the physician of any problems with past due accounts and collections. Especially for physicans just coming into practice, a guaranteed income without any worries about collection expenses seems very attractive. The Personal Care Plan also offers the physician the ability to retain his own fee for service patients and his own independence by operating out of his own office. He remains independent in the hiring of his own office staff, the internal office management, and may exercise his own practice style. This is in sharp contrast to the Kaiser model of HMO in which the physician sees only those patients who are subscribers to the HMO in a clinic building that is owned by the HMO with the clinic policy being controlled by the HMO.

Another very real advantage to the Blue Cross/Blue Shield plan is that it places the primary care physician at the entry point to the health care system. By this very fact, the primary care physician can take care of 80-90% of the usual health care needs of any individual. In theory anyway, this would cut down on unnecessary referrals to specialists for a problem that could be handled by the primary care physician. Any patient who wished a referral would have to have the approval of the primary care physician before any subspecialty or specialty referral or self referral could be done in order for the patient to receive reimbursement from the plan. In the traditional system of health care delivery in this country, patients may seek entry to the health care system at any level they wish. The way the Blue Cross/Blue Shield plan is set up, it should serve to cut down on unnecessary tests, procedures, referrals, and hospitaliztions. At least in theory, this should provide an overall decrease in health care costs. There is the added advantage to the patient over the traditional health insurance coverage

"I have the simplest of tastes . . . I only want the best."

— *Wilde*

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of a more comprehensive coverage being provided at what is usually a reduced cost. The Blue Cross/Blue Shield Personal Care Plan provides a very extensive and comprehensive list of medical services which few traditional health insurance policies can rival.

There are, however, several disadvantages to the Blue Cross/Blue Shield plan as well as most other HMOs no matter what model they are organized under. First, for the physician, I think there is a significant loss of independence. Both the personal care physician and the medical subspecialist lose the freedom to set their own fees. The physician and the patient also lose their freedom to choose which medical specialist they want at the time of referral. Any referral must be made to a medical specialist who is a member of the Blue Cross/Blue Shield Personal Care Plan. The patient loses his ability to choose any physician in the community. I think inherent in this type of health care delivery system is a general loss of freedom of how the individual will practice medicine.

I also am greatly concerned about the issue of quality of care. Although each of us would like to think that he would refer any patient without hesitation if a referral was needed or if a hospitalization was necessary, under the Blue Cross/Blue Shield program the physician is actually encouraged financially not to refer to the medical specialists, not to do various tests, and not to admit the patient to the hospital. Traditionally, these decisions have not affected the primary care physician monetarily, but with this plan the physician would be intimately involved and a conflict of interest is already established. Not only is there a reward for less testing, less referrals, and less hospitalization, but there is also a reward for spending less time with the patient. I think this type of plan would change the traditional way that Internal Medicine is practiced. Traditionally, Internists have prided themselves in being able to spend an adequate amount of time to do a very thorough and complete assessment of a patient. The Personal Care Plan does not provide any financial reward for spending the time it sometimes requires to complete a very thorough evaluation of a patient's problems. This is perhaps the most disturbing aspect of the Personal Care Plan. The financial pressure on each primary care physician would be to see as many patients as he could in a given amount of time. Another disturbing fact about the Personal Care Plan is that the medical specialist is paid on a fee-for-service basis. For every procedure he performs he gets paid and the more procedures he does, the more he gets paid, whereas the primary care physician's fees are limited and fixed. No matter how much time he spends with the patient, he still gets paid exactly the same amount. This seems to again be a system that rewards physicians who perform procedures and specific tasks and does not reward cognitive skills on the part of the primary care physician. All the pressure seems to be laid on the primary care physician to cut costs. He must cut costs by reducing referrals, reducing tests, reducing the amount of time he spends with a patient, and reducing the number and length of stay of hospitalizations. None of this pressure is placed on the medical specialist. He still gets a fee for service, he has no incentive to do less procedures or less testing, but in fact will get paid more for each additional test or procedure that is done.

I think the Blue Cross/Blue Shield Personal Care Plan does address some of the problems of health care delivery that we face in our society. It does stress reduction of the overall health care costs and does provide an increase in the amount of coverage patients receive compared with traditional health insurance policies. It furthermore returns the primary care physician back to the entry point into the health care system. However, I think many of the disadvantages of this program outweigh the advantages. There is the continued problem of providing little reimbursement for cognitive skills and yet continuing to reward the medical specialist who performs numerous procedures. There is the very real question of continuing to provide a high quality of care to patients and yet being forced by the system to spend less time with patients. I fear that there might be a tendency not to do tests which may be warranted, not to admit patients who need hospitalization, and not to refer patients who need referral. I generally dislike the idea that we as physicians are being forced to conform to the HMO brand of medicine just to provide for our continued survival in years to come.

SPECIAL ARTICLE

Asheville: The Tuberculosis Era

Irby Stephens, M.D.

• *A short history of the rise and decline of tuberculosis sanitaria and experts in Asheville between 1871 and the 1950s.*

ONE hundred years ago Asheville was rapidly gaining prominence as a vacation and health resort, and within the space of a few years became the nation's largest and most famous center for the treatment of tuberculosis. To the medical historian, and to the student of tuberculosis in particular, the transformation of Asheville from an obscure mountain village to a world-renowned and major medical treatment center is a fascinating story.

At that time, tuberculosis was the most dreaded disease throughout the world and the leading cause of death in the United States. The ravages of "the White Plague," as tuberculosis was sometimes termed, were especially severe in the crowded, rapidly growing cities, relatively uncommon in the rural areas, and especially rare in the thinly populated mountain regions of Europe and the United States. Patients with consumption placed at rest and exposed to the cool, pure mountain air began to gain weight and strength, their pulmonary lesions showed evidence of healing, and the improvement was often miraculous. This gave rise to the climatic theory of the treatment of pulmonary disease, a theory orginating in Germany and Switzerland and soon adopted and enthusiastically embraced by physicians in America. Physicians and patients everywhere rejoiced that, for the first time, there was a reputable therapeutic approach to pulmonary tuberculosis — a bright ray of hope in a previously dismal scene. In all the eastern United States, Asheville offered the best combination of altitude, atmosphere, and climate considered essential in the treatment of lung disease. As a result, a group of highly competent and dedicated physicians found their way to Asheville to devote themselves to treating and studying tuberculosis, specializing in phthisiology. In a day when specialization was extremely uncommon, these men and their successors became the nation's most highly regarded and most renowned experts in the field of tuberculosis. For 50 years patients by the thousands flocked to Asheville seeking the promise of health offered there.

Beginning about 100 years ago, there was a concurrent and more scientific approach to the treatment and control of tuberculosis. In 1882, Robert Koch discovered the tubercle bacillus. Koch's discovery, paired with the introduction of immunotherapy by Jenner and Pasteur, suggested the possibility of specific methods for the treatment and control of tuberculosis, stimulating widespread research in the field. One of the early laboratories engaged in this effort was established in Asheville.

For 50 years, beginning around 1885, Asheville served as a stage for the dramatic triumph of medicine over the foremost killer of the time. The stage setting and the actors in this drama will hold the attention of any audience with an interest in that singular epoch in the history of medicine.

The Pioneers: Gatchell and Gleitsmann

In 1871 The Villa, a sanitarium exclusively for patients with tuberculosis, was established in the village of Forest Hills (now the Kenilworth section of Asheville) by Dr. H. P. Gatchell, a professor from Hahnemann Medical School. He was joined by his brother, and the doctors Gatchell soon moved The Villa to Haywood and College Streets (now downtown Asheville) where they operated for two or three years, then abruptly abondoned the project and moved away. The reasons for the Gatchells' closing their sanitarium are obscure, but the event was highly important medically, as it was the first tuberculosis sanitarium in the United States, antedating the more famous Trudeau Sanitarium at Saranac Lake, New York, by more than 12 years.

Very shortly after the departure of the Drs. Gatchell, a second and more sustained effort to establish Asheville as a tuberculosis center was made by a highly capable and enthusiastic pulmonary disease expert, Dr. Joseph W. Gleitsmann. Born and educated in Germany, Gleitsmann was a convincing exponent of the European-inspired theory of the benefit of altitude and climate in the treatment of tuberculosis. After a systematic study of the climatic features of the United States, he selected Asheville as having an optimum combination of barometric pressure, temperature, humidity and sunlight believed to be conducive to the healing of the pulmonary lesions of the disease.

Gleitsmann moved from Baltimore to Asheville in 1875 and established The Mountain Sanitarium for Pulmonary Diseases located in the old Carolina House on North Main Street (now Broadway) just south of Woodfin Street. He later acquired an adjoining building to house his patients, who for the most part were referred by prominent physicians in the eastern and southeastern United States. With evangelistic zeal, Gleitsmann (a remarkably vigorous and forceful personality) addressed medical gatherings and published scientific papers extolling the benefits of the Asheville climate. He distributed copies of his papers published in many of the leading medical journals by the thousands to physicians and lay groups throughout the eastern United States.

Dr. Gleitsmann's accomplishments, moreover, were appreciated and recognized by highly competent medical

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From 54 Sunset Parkway, Asheville 28801.

authorities of that day. Among these were Dr. Stanford E. Chille, Professor of Physiology and Pathological Anatomy in the Medical Department of the University of Louisiana. Chille himself on visits to Asheville in the 1870s had been impressed that no tuberculosis had been found in the native population and had recommended Asheville to a number of his tubercular patients. He visited Gleitsmann in Asheville and in a paper before the New Orleans Medical and Surgical Society reported and extolled his work. Dr. Fred Loomis of New York, patron of Dr. Trudeau, referred patients to Gleitsmann's Mountain Sanitarium, and none other than Dr. Lawrason Brown, successor to Dr. Trudeau and recognized historian of clinical tuberculosis, credits Gleitsmann with establishing the first tuberculosis sanitarium in the United States. For five years, Gleitsmann worked unflaggingly, maintaining a census of 20 to 30 patients in his small sanitarium, publishing enthusiastic progress reports and distributing them widely.

It appears, however, that Gleitsmann's enthusiasm and his dream of converting Asheville into a Mecca for tuberculosis sufferers were not shared by the local citizens. In 1880 when he attempted to expand his operation, he found his efforts to obtain more adequate quarters thwarted by local property owners who apparently feared the introduction of tuberculosis into their city and the possible adverse effect on property values. Unable to procure a building suitable for a sanitarium, he tried for one more year to house his patients in the Eagle Hotel located on South Main (now Biltmore Avenue) between Eagle and Sycamore Streets. Finding this arrangement unsatisfactory, he gave up and went to New York, giving as his reason for leaving the lack of facilities. There are no records available that adequately document these events, and we must rely upon conjecture to explain the failures of these early ventures. It is very possible that the Teutonic personalities of Drs. Gatchell and Gleitsmann did not mesh well with those of the predominantly Scotch-Irish mountain people. It may be that, being homeopathic physicians, they were not well received by the Asheville doctors, but in the words of Dr. Gaillard S. Tennant who recalls that era, "as it was, Gleitsmann probably did more than any other one man to bring this place into notoriety, for since his time the stream of travel here has been continuous."

The Beginnings: Battle and Von Ruck

Nothing is more characteristic of pioneers than that they are ahead of their time. Pioneer efforts often fail initially because they are premature. This was undoubtedly true of Gatchell and Gleitsmann, for Asheville in the 1870s was a remote, relatively inaccessible mountain village where communication was difficult and travel uncomfortable.

This was soon to change. Emerging from the post-Civil War depression years, Asheville in the 1880s was ripe for development. It was a small mountain village of 700 in 1870. On receiving its charter as a city in 1883, it had grown into a thriving boom town of 3874 (2808 with 1066 "colored"). The stimulus for this spurt of growth was the advent of the railroad. The Western North Carolina Railroad, which in 1871 had terminated at Old Fort, finally reached Asheville in September 1880, providing access from Spartanburg, Atlanta, and Charleston. In 1883 the line was extended to Knoxville, connecting with the railroad system serving east Tennessee, Georgia, Virginia, and Ohio. Trade immediately flourished and with schedules providing overnight service from points as distant as Louisville and Atlanta, visitors came in increasing numbers to enjoy the beautiful mountain scenery and incomparable summer climate.

In this fertile soil, the seeds planted by Gatchell and Gleitsmann at last began to spring up and, tended by capable men who soon followed, began to thrive and to transform Asheville into a medical center destined to be famous for the next fifty years.

The years 1885 and 1886 were especially notable ones for Asheville medicine in that they marked the arrival of two of the most influential men ever to appear on the local scene: Dr. S. Westray Battle and Dr. Karl Von Ruck. These two outstanding physicians were to pick up the pieces left by Gatchell and Gleitsmann, and each in his own way began to build Asheville into a nationally known center for the treatment of tuberculosis.

The two men could not have been more different. Dr. Battle (figure 1), the very essence of the Southern aristocrat, courtly, elegant, and strikingly handsome in his gray Vandyke beard and fashionable attire, was endowed with irresistible personal charm. A graduate of the University of

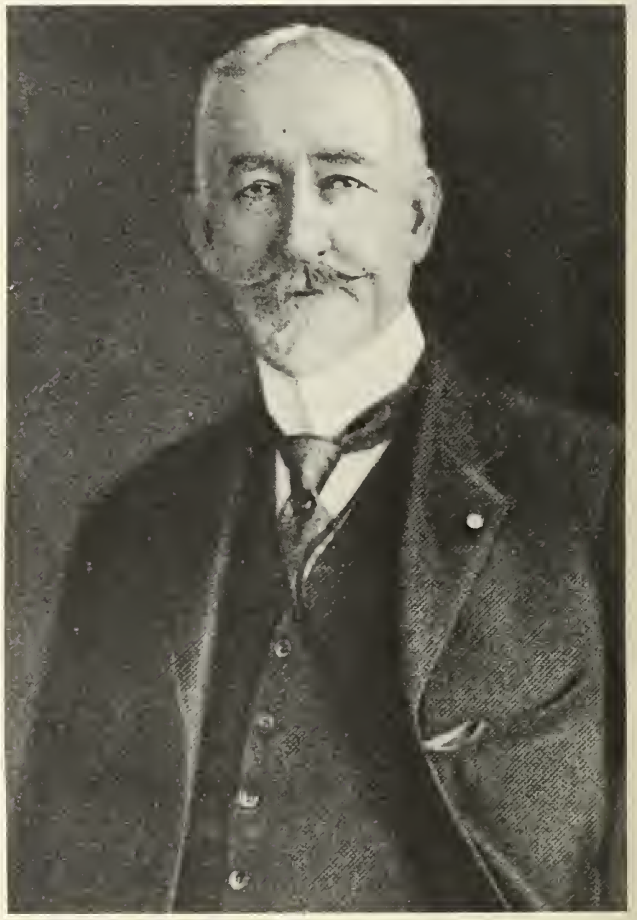

Figure 1. *S. Westray Battle, M.D., outstanding Asheville physician of the 1890 era whose enthusiasm and personal charm attracted many influential individuals, contributing to Asheville's fame and growth.*

Virginia, he studied medicine in New York and attained an M.D. degree from Bellvue Medical College. He started his career as a naval surgeon but was forced to retire because of injuries incurred on sea duty. He decided on a career in private medical practice and became especially interested in the field of tuberculosis. A firm believer in the theory of climato-therapy, he had made his own study of the eastern United States before selecting Asheville as the ideal area for the treatment of pulmonary disease. Having arrived in Asheville in 1885, within three years he had become her most ardent promoter. Dr. Battle's unreserved enthusiasm for his adopted home is manifest in his paper read before the county medical society in 1888 entitled "Climate and the Climatic Treatment of Diseases with Special Reference to the Merits of the Asheville Plateau." He stated that there is "nothing like it East of the Rockies," and concluded that Asheville's climate is "tonic, invigorating, and bracing." He also attributed an almost antiseptic quality to the air, in that "the conditions which seem to favor germ propagation and prolong the species of the genus *Bacterium* do not exist here."

Battle's professional accomplishments were modest but his influence was enormous. A widower for many years, he lived at the old Battery Park Hotel where he was a highly visible and valuable asset to the community: "he was a gifted speaker on any occasion. His diction was polished; his phraseology carefully chosen. Possessed of sparkling and pungent wit, he was at his best as an after-dinner speaker. He was a raconteur blessed with an unusually retentive memory." This portrait, quoted from the *Asheville Citizen* of April 30, 1927, at the time of Battle's death, reveals vividly the impact of the personal appearance of this fascinating man: "Strikingly individual in all things, Dr. Battle was particularly so in his attire. He never followed fashions; he set his own, and no matter what he wore, it always seemed a part of him, rather than an external decoration. His favorite headgear, outside of the formal evening silk "topper," was a soft felt hat of the wide-brimmed variety. In winter he wore a cape, reaching almost to his knees. A white flannel suit, with a black silk sash in lieu of a waistcoat, was his usual summer attire. In evening clothes, of masterful cut and fit, he was in truth the glass of fashion and the mold of form. Always he carried the small rattan cane so popular with English and Indian army officers. . . . Dressed with meticulous care, with pointed mustachios, carefully trimmed Vandyke, and a military air withal. With a cape and cane swinging as he came down Battery Park hill, across Haywood and up the avenue, is it any wonder that fellow members sitting in the windows of the old Asheville Club watched him with admiring interest?"

Dr. Battle's tremendous enthusiasm for Asheville, which he communicated widely among his numerous influential connections throughout the eastern seaboard, brought to Asheville many wealthy and enterprising individuals. These not only added lustre to the Asheville scene, but many, captivated by the climate and scenery, returned to become prominent residents and to use their wealth and vigor to enrich the area. Mrs. W. H. Vanderbilt, suffering from chronic malaria acquired on her travels, came to Asheville under Dr. Battle's care. Her son, George H. Vanderbilt, fascinated by the area, returned to build the Biltmore House; Dr. Battle is reported to have been helpful in acquiring some of the land for Vanderbilt's Biltmore Estate. E. W. Grove of St. Louis, troubled by a bronchial complaint, was another of Dr. Battle's patients who played a major role in the growth and development of the city. Mr. Grove was so impressed by the area that he levelled Battery Park hill, considered an engineering miracle of that day, and built the present Battery Park Hotel. The street in front of his new hotel, Grove named, appropriately, Battle Square for his esteemed physician and friend. Grove went on to develop a new residential section in the north of the city, the Grove Park section, and with his son-in-law, Fred Seely, built the still famous Grove Park Inn.

Throughout a long career, Dr. Battle was Asheville's leading physician and a leader in most of the city's civic and social activities. He founded North Carolina's first chapter of the American Red Cross. After the war, he was chairman of North Carolina's Commission for Relief in Belgium, and was decorated by that country for his services. He was active in North Carolina's National Guard, served as its Surgeon General, and rose to the rank of brigadier general. Still very active at seventy-two, he died while attending a meeting in Raleigh, April 29, 1937. His impressive home on Macon Avenue still stands, now occupied by the WLOS-TV station.

Dr. Karl Von Ruck, on the other hand, was a near recluse, a dedicated scientist interested almost exclusively

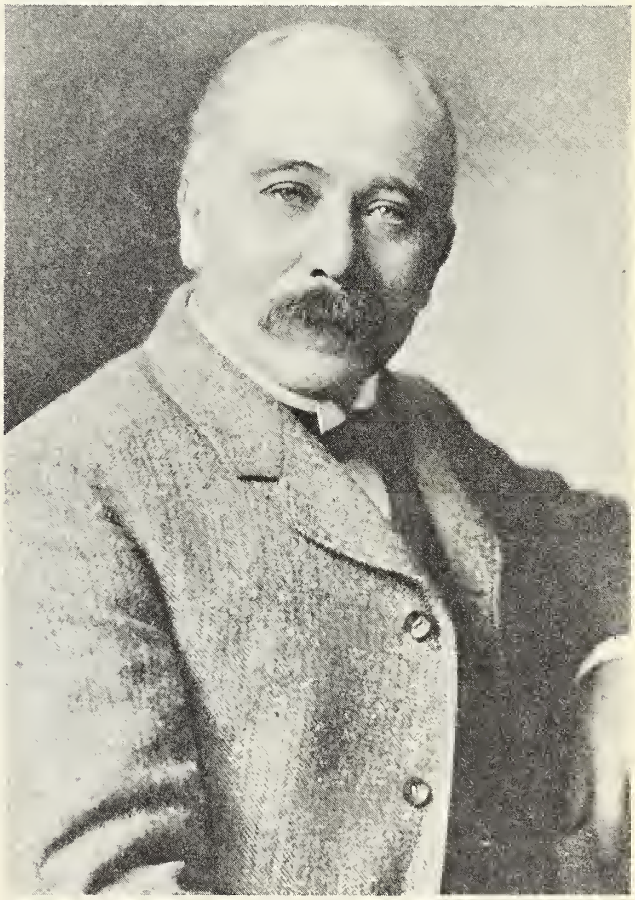

Figure 2. *Karl Von Ruck, M.D., aloof and controversial physician-scientist who initiated the sanitarium era in Asheville.*

in medical research. He was born in Constantinople, the son of a German diplomat, and was educated in Germany, B.S. University of Stuttgart, M.D. University of Tubingen. He came to the United States and received a second M.D. degree from the University of Michigan in 1879. Interested in tuberculosis since his student days, he was present at the famous 1882 meeting in Berlin when Robert Koch announced the discovery of the tubercle bacillus. Von Ruck closed the medical practice he had begun in Ohio and thereafter devoted himself entirely to the study of tuberculosis. Possibly influenced by Gleitsmann's reports, he came to Asheville in 1886 to start a sanitarium and conduct experimental work on tuberculosis. In 1888, a memorable date in Asheville's medical history, Karl Von Ruck established the Winyah Sanitarium (figure 3), which proved to be highly successful both professionally and financially. In 1902, he was joined by his only son, Silvio, who had also become a pulmonary disease specialist. Silvio took over the operation of the sanitarium and Von Ruck was able to devote himself entirely to his studies. A brilliant and educated man, Von Ruck was not only a scientist but a scholar as well. He founded and edited *The Journal of Tuberculosis*, the first medical journal devoted entirely to that disease. Published quarterly, it contained papers contributed from leading experts in the field from all over the world. He amassed a large library and carefully abstracted on card files the entire world literature on tuberculosis, most of which at that time was in German. After his death, this invaluable catalogue was purchased by the Army Medical Library, then America's largest medical reference source.

Since his student days in Germany, Von Ruck had been interested in research. Exciting and momentous discoveries emanating form the laboratories of Pasteur, Koch and others in Europe gave promise that infectious diseases might be prevented and treated by injecting vaccines made from the newly discovered microbes found to be the cause of these diseases. In 1890, on receiving a cablegram announcing the discovery of tuberculin, Von Ruck caught the first available steamer to Europe in order to visit Koch's laboratory and to study his methods. Koch himself provided Von Ruck with a vial of tuberculin to bring back to Asheville and use in his own investigations. Von Ruck realized that if a potent vaccine could be perfected, tuberculosis, the greatest scourge of the civilized world, could be prevented, possibly eliminated. Undeterred by Koch's initial failure with tuberculin, Von Ruck devoted his entire time and energy toward developing an effective antituberculosis vaccine. In 1885 he formed the Von Ruck Research Laboratory and was joined by Dr. Edwin Klebs, one of the world's outstanding bacteriologists, who was involved in a similar project. Klebs did come up with a vaccine which he called antiphthisin, but he left Asheville after two years to become the professor of pathology and bacteriology at Rush Medical School.

Von Ruck worked on and succeeded in producing a vaccine, a watery extract of tubercle bacilli which he thought superior to any of the previous preparations. He and his son at once set about to test its effectiveness both in preventing tuberculosis in children and as an adjunct in treating adult tuberculosis. After more than ten years of extensive but largely uncontrolled clinical trials, he published his results in the *Journal of the American Medical Association* May 8, 1911, in a paper entitled "A Practical Method of Prophylactic Immunization against Tuberculosis," claiming success not only in immunizing children against tuberculosis but also in using the vaccine to treat those who had already contracted the disease. He concluded his paper as follows: "These studies I am continuing, and I hope that others will take them up also. All I feel justified in claiming at this time is that I am the first to have made a successful advent in this most important and promising field of prophylaxis in a disease that leads in the mortality statistics of the human race."

In 1914 he presented the results of his research to an international conference in London and his ideas were favorably received. Tragically, the outbreak of World War I forced the cancellation of clinical trials of his vaccine in England and Europe, and in the turmoil of a world at war his work was shelved and forgotten.

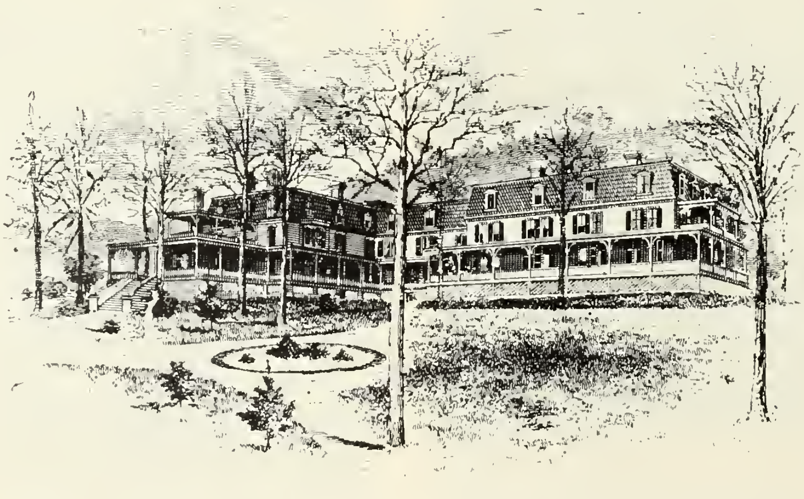

Figure 3. *Winyah Sanitarium, 1896. Artist's sketch of Von Ruck's first Asheville sanitarium.*

Doggedly he continued, and in 1916 in conjunction with Silvio published "Studies on Immunization Against Tuberculosis" in which he described the method of preparation of the vaccine and made further claims of benefit from the material. To his great disappointment and chagrin, Von Ruck's work failed to find wide acceptance among his colleagues. In fact, he was subjected to a great deal of criticism and ridicule, difficult for a man of his nature to tolerate.

In 1918 Silvio Von Ruck went to New England to administer the vaccine to children in a large orphanage as part of their study. He contracted influenza and died two days later in New York City. Silvio's daughter, Von Ruck's only grandchild, also contracted the disease and died within forty-eight hours on the train back to Asheville. Karl Von Ruck never recovered from this blow, but he lived on in his Asheville mansion another four years. His wife died in 1921, and he died a year later of nephritis at age seventy-three. In 1921, one year before his death, two French bacteriologists, Calmette and Guerin, using, as suggested earlier by Klebs, an attenuated strain of the tubercle bacillus, produced BCG vaccine, the first really effective vaccine against tuberculosis and the one in widespread use today. One cannot discount the value of Von Ruck's years of hard work and his contribution to the field of immunity to tuberculosis. But for Asheville, his great contribution was that he ushered in perhaps the greatest era in Asheville medicine — the era of the great tuberculosis specialists who came to study under Von Ruck, became master clinicians, and were the ones finally responsible for establishing Asheville as the outstanding tuberculosis center in America.

Asheville's Great Tuberculosis Specialists

The fruits of Battle's and Von Ruck's labor were not long in appearing. Several local physicians became students of tuberculosis, soon acquired a mass of experience, and developed considerable expertise in the field. Notable among these were Drs. J.M. Burroughs, L.B. McBrayer, and John Hey Williams. Asheville's future, however, was shaped primarily by several young physicians who came to study under Von Ruck at Winyah Sanitarium. These became the famous "TB" specialists of Asheville.

The first was Dr. Chase P. Ambler of Ohio. Ambler graduated from Western Reserve Medical School in 1889, and on the advice of his dean came to Asheville to work with Von Ruck. Though trained in laryngology and ophthalmology, Ambler was primarily a specialist in pulmonary tuberculosis. Much later, in 1922, he built his own fifty-bed sanitarium called Ambler Heights, which served as a model for similar institutions elsewhere. Over the years several physicians were associated in practice with him, including his son, Arthur C. Ambler, who joined him in 1921. He did not confine himself to his own sanitarium, where he welcomed the other "TB" specialists as members of the staff, but also participated as a leading figure in the other Asheville hospitals of his day. He reorganized the Merriwether Hospital after its founder's death, serving as Chief of Staff and dean of its nurses' training school. He was a consultant at St. Joseph's Sanitarium. In civic and national affairs he achieved even greater fame. Ambler was a naturalist and an enthusiastic sportsman, enjoying hunting, fishing and all aspects of outdoor life. He was a founder of Asheville's Audubon Society and is given credit for initiating laws requiring hunting and fishing licenses in North Carolina and providing for wardens to enforce those laws. A National Park in western North Carolina was suggested by Ambler as early as 1899, and he thereafter devoted a great deal of time and energy toward that end. He pesonally organized the Appalachian National Park Association which later became the American Forestry Association. Mt. Ambler, a 6,000 foot peak in the Smokies along the Appalachian Trail near Newfound Gap is named for him and a plaque in recognition of his contribution to the conservation movement was appropriately placed in "The Cradle of Forestry" located in the lovely Pink Beds of his beloved Pisgah National Forest. His outstanding contributions in the National Park Movement, an idea which he proposed and pursued throughout his life, culminated in 1912 with the purchase by the Federal Government of 50,000 acres of the George Vanderbilt estate to establish the Pisgah National Forest. Dr. Ambler remained a leader in professional and civic activities until the last year of his life. He died of intestinal cancer at his home on Hilltop Road, Biltmore Forest, in June 1932.

Figure 4. *Chase P. Ambler, M.D., Von Ruck's first resident; one of Asheville's early TB specialists.*

Von Ruck's second student, Dr. William Leroy Dunn (figure 5), was to achieve even greater things than his predecessor Ambler. Dunn, also from Ohio, was a brilliant student. A near prodigy, he obtained a degree in pharmaceutical chemistry, then went on to receive an M.D.

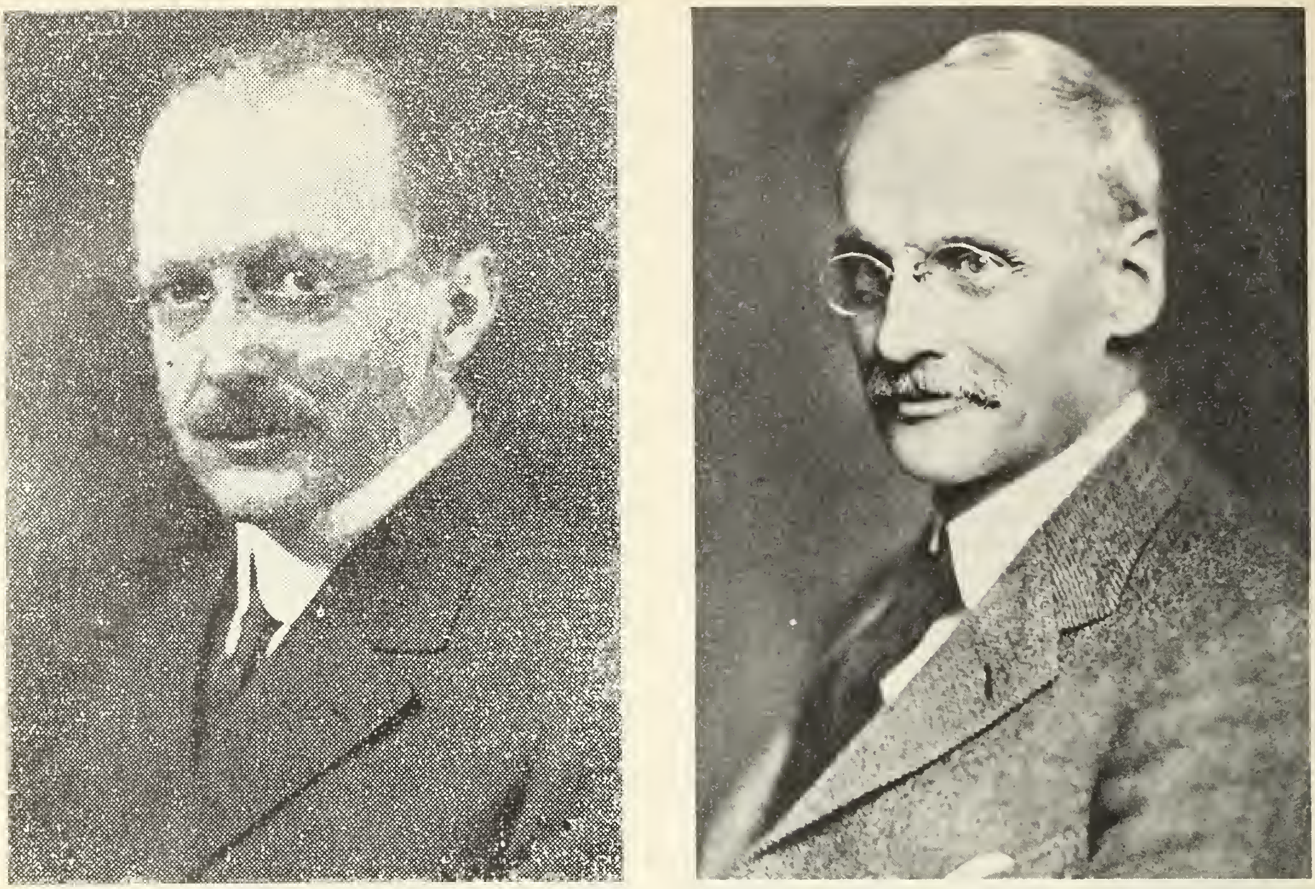

Figure 5. *W. L. Dunn, M.D. (left) and Charles L. Minor, M.D. (right), the two most outstanding of Asheville's many tuberculosis specialists in the early 1900s.*

degree at Michigan University in 1891 when he was only 20 years old. He was required to wait a year until he became 21 to be licensed to practice, so he spent that year and the next as assistant to the Professor of Surgery at Michigan. In 1894 he came to Asheville to work in Von Ruck's laboratory beside the renowned Dr. Edwin Klebs for two years. Upon Klebs' departure in 1897, Dunn went to Europe to study at the great university centers of Leipzig, Berlin, Vienna, and Paris. 1900 found him back with Von Ruck as house physician at Winyah, but shortly thereafter he entered practice for himself, establishing the Dunn Clinic. He was soon recognized as an expert in tuberculosis and his fame became widespread.

Dunn was also a prominent figure in medical circles and he was associated with the leaders in his field in national and international organizations related to tuberculosis. He was honored by election to the prestigious Clinical and Climatological Society and served as its president. In 1916 he was awarded an honorary degree by his alma mater. During World War I, as a colonel in the Army Medical Corps, he was sent on special assignment to Italy and was decorated by the Italian Government for his services to that country. After the war he was asked to serve on several important commissions concerned with the rehabilitation of disabled veterans. He advised on the construction of several veterans' hospitals and it was due to his influence and association with General Hines, chief of the Veteran's Administration, that a permanent center for the treatment of tuberculosis was located near Asheville at Oteen. In 1928, hospitalized with terminal cancer, Dr. Dunn was unable to attend the dedication of the permanent buildings at Oteen and died two weeks later of lung cancer at the age of 57.

Dr. Charles Launcelot Minor (figure 5), a contemporary and later an associate of Dr. Dunn, was a brilliant young man who came to Asheville for health reasons and remained to become perhaps the most outstanding lung specialist of them all. Dr. Minor's credentials were impeccable. Born in New York, he was a descendent of an old and illustrious Virginia family. Educated at Episcopal High School and the University of Virginia, he transferred from academic studies to the Medical School and graduated with honors in 1888. He served as house surgeon at St. Luke's Hospital in New York from 1888 to 1890; then, as was the fashion in those days, he spent two years studying in the hospitals of Vienna, returning to begin practice in Washington, D.C. in 1892. He contracted pulmonary tuberculosis, however, and came to Asheville for treatment in 1895. After 18 months he was considered recovered, but by this time, he had become interested in tuberculosis and spent the rest of his life in that field. He was a remarkably able person, tall, redheaded, impulsive, forceful, energetic and imposing with a brilliant mind and studious habits. He rapidly achieved prominence as a tuberculosis specialist and was a leader in the civic and social life of Asheville. He was also an able scholar, interested in intellectual pursuits ranging from medicine to philosophy. His excellence over a broad field was recognized by his election as an honorary member of both Phi Beta Kappa and Alpha Omega Alpha honorary societies. In the treatment of tuberculosis he stressed the importance of rest, diet, and outdoor living rather than of drugs. He was one of the first to use X-ray in the diagnosis of pulmonary tuberculosis and, later, to employ artificial pneumothorax in its treatment. He was the author of more than 50 papers on the subject of tuberculosis and was selected to contribute the chapter on "Symptoms and Diagnosis" in Kleb's famous textbook *Tuberculosis* published in 1908. Though dissimilar in personality, he and Dunn were close friends and associates. Like Dunn, Minor was active in medical organizations of which he was invariably the leader: Editor of the *American Review of Tuberculosis* for the first two years of its publication; a founder and president of the Southern Medical Association; a member and one-time president of the exclusive Clinical and Climatological Society; and the American delegate to the International Congress on Tuberculosis at its meeting in Brussels in 1919 and in London in 1921. In 1926 the University of North Carolina presented Dr. Minor with an honorary degree in which the citation by Dr. Archibald Henderson reads in part: ". . . he early turned the full current of his eclectic mentality upon the complex problems of tuberculosis, its diagnosis, treatment, and prevention . . . . He ranks today as an authority on that disease without a superior in the entire country. Versatile in attainments, eclectic in tastes, like the later Dr. Weir Mitchell, he has, through the magic of his sympathetic nature and the range of his interest, won alike the unquestioned confidence and ardent devotion of his patients." Still active, Dr. Minor died suddenly of a heart attack December 26, 1928 in his home in Biltmore Forest.

Another Von Ruck protege, Martin Luther Stevens, also an Ohioan, was educated in Baltimore and came to Asheville in 1899 to work under Von Ruck and became the physician-in-charge of the old Winyah Sanitarium when the new one was built on the outskirts of the city, now Spears Avenue, in 1909. He then went into practice for himself, specializing in tuberculosis, and developed an extensive practice. He owned and operated the Strawberry Hill Sanitarium located on the site of the present Rhododendron Park in West Asheville, and he served on the staff of other sanitaria as well, including Ambler Heights and St. Joseph's, where he was at one time chief of staff. Dr. Stevens was a charter member of the National Tuberculosis Association, served on the North Carolina Board of Medical Examiners, and was president of the North Carolina Medical Society in 1930.

During all these years Von Ruck was busy in his laboratory intent on perfecting a vaccine against tuberculosis. He had no interest in clinical medicine and no talent for patient care which he left to his succession of brilliant young residents and later to his son Silvio. Furthermore, Von Ruck was an austere and difficult man who did not get along well with the local physicians (who were somewhat in awe of him) or even with his own colleagues. He is described as a perfectionist, difficult to please, and sparing in his praise. His series of able associates went out to practice on their own. None maintained a close or lasting relationship with their former chief. Von Ruck's name is pointedly missing from the numerous scientific papers published by the Asheville physicians of that period. In like manner, reference to the well-known Asheville phthisiologists is notably absent from the pages of Von Ruck's *Journal of Tuberculosis*. Even his association with Klebs, which held such promise, was a brief and unsatisfactory one.

Winyah Sanitarium continued to thrive under Silvio Von Ruck who, though a competent and attractive young man, never gained the position of esteem accorded to his father. Similarly, none of the subsequent resident physicians at Winyah attained the prominence of the early ones such as Ambler, Dunn, and Stevens. One young man, Dr. C. C. Orr, a Charlotte native, A.B. Davidson, '95 and M.D. Michigan, '04 did remain. He spent a year in chemistry and bacteriology in Von Ruck's laboratory before entering practice in 1907 and subsequently published a number of papers on tuberculosis and related subjects. He remained in active practice in Asheville almost until his death in 1960 at the age of 88. In his later years he practiced general internal medicine.

The Second Generation Specialists

By the early 1900s Asheville had become established as the outstanding tuberculosis center east of the Rockies. To care for the increasing flood of tuberculosis sufferers arriving each year, Asheville's great specialists took on associates who, typically, soon set up practice as TB specialists in their own right. Like their predecessors, many of them came as patients to be treated for tuberculosis and, having regained their health, remained to enter this field of practice. (Interestingly, the same phenomenon occurred at the Trudeau Sanitarium from which numerous pulmonary specialists "graduated," having acquired their first training in chest disease while there as patients with tuberculosis.) There were many outstanding men in this Asheville group. Dr. George Alexander, one-time associate of Von Ruck, after training elsewhere returned to Asheville to practice. Dr. Paul Paquin, friend of Dr. Battle, Professor of Medicine in St. Louis, came to continue investigative work in the field of tuberculosis. Arthur C. Ambler was initially associated with his father at Ambler Heights and later became Asheville's first physician anesthetist. W. H. Pendleton, former superintendent of the North Carolina State Tuberculosis Sanitarium, and the studious Karl Shaffle were both originally associates of Drs. Dunn and Minor. C. D. C. Colby, medical school classmate of Dr. Dunn, joined him in 1915 and helped care for the practice while Dunn was away in World War I. Carl V. Reynolds, one of an old Asheville family, eventually went to Raleigh to serve for many years as one of North Carolina's most esteemed State Health Officers. Dr. John W. Huston started a sanitarium in West Asheville and was active in preventive measures among children. Of the large group of physicians who appeared later on the scene, from 1910 to 1920, three in particular stand out as deserving special mention.

Dr. Paul H. Ringer (figure 6), a long-time associate of Dr. Minor, turned out to be the most outstanding of the

Figure 6. *Paul H. Ringer, M.D., an associate of Drs. Dunn and Minor and the last of the great specialists in Asheville's tuberculosis era.*

second generation tuberculosis experts. A New Yorker by birth, his background was one of culture and learning. His father was a professor of foreign languages, his mother a distinguished musician. He received his A.B. and M.D. degrees from Columbia University and trained at the Roosevelt Hospital. Like so many of Asheville's physicians of that day, he contracted tuberculosis and came to Asheville for that reason. Witty, charming, highly educated, he was in the true tradition of Dr. Minor, with whom he became associated in 1906. He enjoyed a long and illustrious career spanning more than 40 years and was accorded many honors. After serving on the Board of Medical Examiners, he was president of the North Carolina Medical Society 1935-36 and president of the Southern Medical Association 1940-41. Among other honors, he was, like Dr. Minor, a member of the Clinical and Climatological Association, Director of the North Carolina Tuberculosis Association, vice president of The National Tuberculosis Association, and regent of the American Association for Thoracic Surgery. He married an Asheville girl, the daughter of a prominent Asheville family, and entered actively into the civic and social life of the community. He was an Elder in the Presbyterian Church, a member of the Board of the Biltmore Forest Country Club, a director of the Y.M.C.A. and of the Good Samaritan Mission, president of the Community Chest, and the 1937-41 president of the Asheville Music Association, now the Asheville Symphony Society. In 1950 he retired for reasons of poor health and is buried in Riverside Cemetery. At the time of his retirement a resolution in praise of his achievements, passed by his fellow physicians in the Buncombe County Medical Society, characterized him most appropriately as "an ornament to our profession."

C. Hartwell Cocke was the last of the second generation phthisilogists. His story is remarkably similar in many respects to Dr. Charles Minor some fifteen years earlier. He was born in Mississippi, the son of the president of a small college, and attended Episcopal High School where he was the honor student for each of his three years. Like Minor, he graduated from the University of Virginia, but then went to Cornell for his M.D. degree. He interned at the Presbyterian Hospital in New York City 1906-07, following which he studied in London, Paris and Vienna. Just as had Dr. Minor, Cocke trained initially in surgery and practiced briefly in Birmingham, Alabama, but when he developed tuberculosis he came to Asheville to be treated. Following recovery, he decided to specialize in tuberculosis and in association with Dr. John W. Huston started the Zephyr Hill Sanitarium. Dr. Cocke followed the footsteps of Dr. Minor in national medical circles as well as in local affairs. He became secretary of the section on tuberculosis in the A.M.A. and vice president of the American College of Chest Physicians in 1937. He was a prominent figure in the American College of Physicians, serving as chairman of the Board of Governors 1929-42 and Regent 1936-42. He was a vestryman of Asheville's Trinity Episcopal Church for 20 years and was one of the founders of Biltmore Forest Country Club. He was a leading Asheville physician until his death from a heart attack in 1944. Dr. S. L. Crowe, who came in 1926 as Dr. Cocke's associate, is still in active practice in Asheville almost 60 years later.

Appropriately, it fell to a nephew of Karl Von Ruck to be the last of the Asheville tuberculosis specialists. Edward W. Schoenheit, whose father, W. A. Schoenheit, was the business manager at Winyah and whose mother, Grace Moore Schoenheit was Mr. Von Ruck's sister, was born on the sanitarium grounds at Mt. Clare and Dortch Avenues. He first went to the University of Tennessee to study veterinary medicine but, changing careers, transferred to the University of Maryland and was a pre-medical student when his cousin, Silvio Von Ruck, died. He obtained his medical degree from Jefferson, interned at the Pennsylvania Hospital, and returned to practice at Winyah in 1921, just one year before Karl Von Ruck's death. A principal heir of the Von Ruck estate, he inherited the sanitarium, and after his marriage in 1924, he and his wife, the former Elizabeth Kimberly, lived in the Von Ruck mansion off Charlotte Street until 1937 when they built their present home in Biltmore Forest. About 1930, sensing that the tuberculosis era in Asheville was on the decline, Schoenheit closed Winyah and spent a year in Vienna studying cardiology. He returned to enjoy a long and successful career as an internist in Asheville. He was greatly respected by his colleagues, serving as president of the North Carolina Medical Society, and was the recipient of the Distinguished Physician Award in 1976 when he retired after 53 years of practice. He died in 1980 and is buried in the Von Ruck plot at Riverside Cemetery.

Asheville's Sanitaria

In 1900 Asheville's only sanitarium, the Old Winyah, with a capacity of no more than 60 beds, had long since become inadequate to accommodate the horde of tuberculosis patients who came to the now famous resort in ever-increasing numbers. Except for those in Winyah, patients were housed in boarding houses, most of which were operated solely for the care of people with tuberculosis. In a 1901 brochure advertising Asheville, Von Ruck mentions the numerous establishments of this nature available to patients at a cost of as little as $4-$8 per week and ones with "better accommodations" at rates of $10-$15. "A few" says Von Ruck, "refuse invalids altogether," suggesting that most of the boarding houses did accept "tuberculars." The number of "boarding houses" rose from 55 in 1900 to 137 in 1910 and remained at that level for the next 20 years. These were for the most part large houses converted into small sanitaria providing room, board, and bedside nursing care. The ever-present open air sleeping porch was a necessary feature common to all. Usually the physicians arranged accommodations for their patients, which had the effect of clustering patients in particular locations, all cared for by one physician or his associates. Some physicians opened sanitaria of their own, some quite large and attractive two and three story buildings with the ubiquitous open air porches. In 1900 three nuns from Belmont Abbey converted a former school house at 40 North French Broad into "St. Joseph's Retreat," which provided 18 beds for patients with tuberculosis. In 1905 it was moved to larger quarters on Starnes Avenue and then in 1916 to its present location on Biltmore Avenue, where it became the St. Joseph's Sanitarium with 95 beds, subsequently the St. Joseph's Hospital of today.

The slopes of Sunset Mountain quickly became studded with sanitaria. By 1905 Dr. Dunn had added "Sunnyside" operated by his parents on Sunset Drive. Miss Ann O'Connel, a retired Johns Hopkins nurse, operated Edgewood Cottage in Dr. Porter's old summer home. The largest of the group, "Fairview," was run by a Mrs. Perkins, who cared for as many as five hundred patients housed in small 2- to 4-bed "shacks" (a Trudeau Sanitarium term): tiny buildings open on the sides above window level except for rolled down curtains. They were outfitted in Spartan fashion with only beds, a stove, and an enclosed bathroom. Food was prepared in a large central building and care was provided by a staff of 50 or 60 nurses and attendants. Mrs. Perkins was afforded great respect because she cared for patients regardless of their financial status and admitted all referrals, many of whom were unable to pay. Other such installations built in this favorite area were Onteora Cottage, Sunset Heights, and Roye Cottage, the latter of which was still in operation in the 1950s.

Because of the desire for open air (as well as the attitude of the townspeople), the sanitaria were located at edges of town, but as the city grew, many came to lie within the corporate limits; for instance, the new Winyah on Spears Avenue, the Wellington and the Elmhurst on Edgewood Road, and the Oakland on Victoria Road — all originally located beyond the city limits. With the advent of the automobile, additional facilities were built further out, such as Ambler Heights on the Swannanoa Road, Hillcroft and Abernathey Cottage south of Biltmore Village, Violet Hill and Zephyr Hill in West Asheville, and others as far away as Fairview and Black Mountain.

Asheville flourished in the good times of the 1920s, but Dr. Schoenheit's estimate of the future of private sanitaria proved to be accurate. In 1930 the business community, prompted by the economic reverses of the Great Depression, belatedly recognized the value of the tuberculosis trade. *Health and Happiness in the Land of the Sky,* a promotional magazine published in 1930 by the local Chamber of Commerce with the approval of the Buncombe County Medical Society, boasted twenty tuberculosis specialists and twenty-five sanitaria providing 900 beds for patients. The sanitarium rates in the depressed market of that day ranged from $15 to $35 a week while the more luxurious Winyah and Ambler Heights commanded $50 a week (physician's fees not included).

Times were changing rapidly, however. State sanitaria manned by fulltime professional staffs had sprung up throughout the nation, new and improved methods revolutionized the treatment of tuberculosis, and the days of the private sanitaria were over. In nearby Oteen, a thousand-bed modern sanitarium, the largest such facility in the nation, offered superior care at no cost for war veterans. In 1937 the state opened a branch of the North Carolina system in Swannanoa, later named the Western North Carolina Sanitarium, offering excellent care at a rate of 50¢ to $1.50 per day including medical fees.

One by one the Asheville sanitaria closed. In 1937 the Sisters of Mercy enclosed the sleeping porches at St. Joseph's and converted it into a general hospital. A few remaining cottage-sized facilities remained as late as the 1950s. All were gone by 1960. By that time, with the introduction of antibiotic therapy, sanitarium care was rarely needed. In 1959, with fewer than 60 patients with tuberculosis, Oteen itself was converted to a center for pulmonary and cardiac surgery, and by 1979 the Western North Carolina Sanitarium, no longer needed for tuberculosis, became a drug detoxification unit and a home for the mentally retarded. By the 1940s the only physicians specializing in tuberculosis were the full time staff of the state-supported sanitarium. There were none in Asheville. The tuberculosis era had come to an end.

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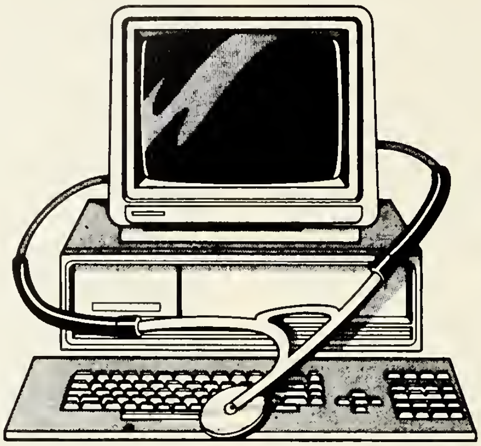

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PHARMACOTHERAPY

Serum Digoxin Levels and Renal Failure

Daniel L. Dolan, M.D. and C. Edwin Webb, Pharm.D.

• *The authors measure and report serum digoxin levels in patients with renal impairment and compare techiques for measuring digoxin levels.*

THE commonly employed methods for quantification of serum digoxin concentration include radioimmunoassay, enzyme immunoassay and fluorescent polarization immunoassay. Measurement of the serum digoxin concentration is often helpful in the management of certain patients, is particularly important in young or elderly patients and in any patient with significant renal impairment, since these groups have been identified as being at risk for digoxin toxicity.[1,2]

Recently, reports have appeared demonstrating elevations of the serum digoxin concentration in patients with renal impairment who were not receiving digoxin.[3-5] The authors have suggested the possibility of a cross-reactivity of the assays with some unidentified digoxin-like substance, and have reported apparent variations in this effect from one assay method to another.

These reports prompted us to examine data on patients in our community having chronic renal failure who were not taking digoxin. In addition, since the two major hospitals in Asheville employ different analytic techniques for digoxin measurement, we were able to study potential differences in these two methods.

Blood was obtained from 26 patients in chronic renal failure before and after routine outpatient hemodialysis. Simultaneous serum creatinine determinations were made (table 1). No serum creatinine value in any specimen fell below 3.3 mg/dl. Each specimen was divided, then analyzed by both the Fluorescence Polarization TDX (Method A) and the Gammacoat I 125 Digoxin Radioimmunoassay (Method B). Patient 25 was taking digoxin and served as a control. The remainder received no digoxin, as determined by analysis of chart records and medication history information.

Under routine clinical conditions, the two hospital laboratories report quantitative values only when in excess of 0.5 ng/ml. Quantification below that level is possible with Method A using simple dilution techniques, and values are reported here for interest. Values described as "low" in Method A represent values ≤ 0.01 ng/ml. Method B employed a 0.5 ng/ml standard; hence numerical values below that were reported as zero. All serum samples were immediately frozen upon collection and all analyses were performed within 72 hours. No patients were receiving concurrent spironolactone, furosemide or steroid therapy at the time of this study.

Results of the analysis are listed in table 1. Both methods correctly identified the patient on digoxin. With this exception, no value of any specimen exceeded a digoxin concentration of 0.23 ng/ml.

Graves et al reported on serum digoxin concentrations in aliquots of sera from 54 patients with serum creatinine values in excess of 2 mg/dl and found considerable discrepancy among six radioimmunoassay methods.[4] In this study most values fell below the usual clinically reportable level of 0.5 ng/ml. However, the highest measured concentration was 1.0 ng/ml by radioimmunoassay and included

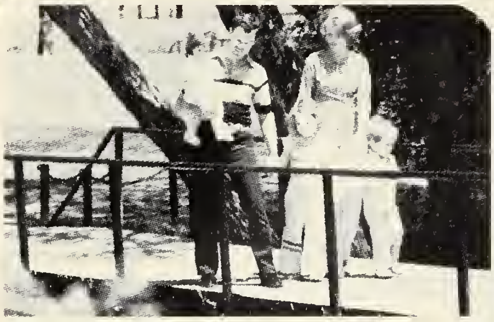
Table 1

Measurements of serum creatinine and digoxin concentrations in 26 patients with chronic renal failure.

Patient	Serum Creatinine Before Dialysis/ After Dialysis (mg/dl)	Serum Digoxin Method A Before Dialysis/ After Dialysis (ng/ml)	Serum Digoxin Method B Before Dialysis/ After Dialysis (ng/ml)
1	9.0/4.2	0.12/0.09	0.0/0.0
2	10.1/4.5	low/0.23	0.0/0.0
3	18.5/14.4	low/0.11	0.0/0.0
4	16.5/9.2	0.03/0.5	0.0/0.0
5	11.3/6.5	low/0.17	0.0/0.0
6	11.2/6.8	0.04/0.19	0.0/0.0
7	13.0/6.1	low/low	0.0/0.0
8	12.0/4.4	0.21/0.04	0.0/0.0
9	14.9/9.0	0.07/0.15	0.0/0.0
10	11.2/6.3	0.13/0.05	0.0/0.0
11	9.8/7.7	0.03/low	0.0/0.0
12	20.0/10.8	0.17/low	0.0/0.0
13	10.6/6.3	low/0.21	0.0/0.0
14	13.6/5.5	0.01/0.16	0.0/0.0
15	7.9/5.4	low/low	0.0/0.0
16	13.2/5.7	low/0.05	0.0/0.0
17	8.6/6.0	low/low	0.0/0.0
18	17.5/9.2	low/low	0.0/0.0
19	15.5/7.4	low/low	0.0/0.0
10	16.3/9.6	low/low	0.0/0.0
21	12.5/5.9	low/low	0.0/0.0
22	7.7/4.3	0.13/low	0.0/0.0
23	9.1/3.3	low/low	0.0/0.0
24	9.4/6.0	0.09/low	0.0/0.0
25*	3.7/—	0.91/—	0.79/—
26	9.7/4.5	0.03/0.14	0.0/0.0

*Patient was taking digoxin.

From the Departments of Internal Medicine and Pharmacy, Mountain AHEC, Asheville 28801 and The Schools of Medicine and Pharmacy, The University of North Carolina, Chapel Hill 27514.



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values of 0.6 and 0.7 ng/ml in other sera by both this method and EMIT-CAD, an enzyme immunoassay. One level of 0.58 ng/ml, along with a spread of levels between 0 and 0.48 ng/ml was seen with the Gammacoat assay. Use of the Raimen Digoxin RIA Kit resulted in levels between 0 and 0.52 ng/ml. The Digoxin Radioimmunoassay Kit gave levels below 0.05 ng/ml except for one value of 0.32 ng/ml. Levels measured by the Immunophase techniques also clustered below 0.05 ng/ml except for one value of 0.46 ng/ml.

Previous reports of spurious values have raised concerns regarding the interpretation of serum digoxin concentrations in patients with renal failure. While the magnitude of these levels is frequently quite small and clinically insignificant, the potential addition of these values to true digoxin content in a patient taking digoxin could lead to a misinterpretation of the value with a corresponding decision to under-dose. The relatively few high spurious levels, when present, could indeed lead to clinical confusion, and may perhaps explain the rise in serum digoxin concentration over an 11-day period reported by Gault et al following a total dose of 1 mg of digoxin administered intravenously over 3 days in a patient with acute renal failure.[6] Similar types of cross-reactivity have been reported in pregnant patients,[7,8] and neonates [9,10] not taking digoxin. The differences between commercial kits may be related to the specific antibody employed and its tendency toward cross-reactivity.

Our data in a series of 26 patients did not contain any spurious serum digoxin concentrations above 0.23 ng/ml by either method, a value considerably below what would be routinely reported. Yatschoff et al reported values by the Abbott TDX and Kallestad methods to be less than 0.28 ng/ml in 25 uremic patients, although a few false positives were seen in 30 neonates.[9] Similar results in neonates have been reported with the Gammacoat method.[10] We chose not to include neonates in our evaluation.

We conclude that the risk of false positive serum digoxin levels by the Abbott TDX and Clinical Assays Gammacoat methods was acceptably small in our population with chronic renal failure. While the possibility exists that the contribution of a spurious value may occasionally lead to pharmacokinetic misinterpretation and possible inadequate dosing of digoxin in a patient with renal failure, clinical and hemodynamic evaluation of the patient should provide the additional data necessary to make appropriate therapeutic decisions.

Acknowledgment

We wish to thank H. Denniston Crews, M.D., Asheville Kidney Center; John McCleod, M.D., Memorial Mission Hospital; and Henry Garfield, Ph.D., St. Joseph's Hospital for their technical assistance in this study.

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Brief Summary of Prescribing Information
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See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information A Brief Summary follows

DESCRIPTION

Norlestrin Products are progestogen-estrogen combinations

INDICATIONS AND USAGE

Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0 05 per 100 woman-years, in clinical trials with Norlestrin 2 5/50 involving 96,388 cycles, there was a pregnancy rate of 0 22 per 100 woman-years

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance

CONTRAINDICATIONS

1. Thrombophlebitis or thromboembolic disorders
2 A past history of deep-vein thrombophlebitis or thromboembolic disorders
3 Cerebral vascular or coronary artery disease
4 Known or suspected carcinoma of the breast
5 Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding
7 Known or suspected pregnancy (See WARNING No 5)
8 Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1 *Thromboembolic Disorders and Other Vascular Problems* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2 0 times greater in users than nonusers, and the risk of thrombotic stroke was 4 0 to 9 5 times greater

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not Oral contraceptives, however, were found to be a clear additional risk factor

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders Should any occur or be suspected, the drug should be discontinued immediately

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization

2 *Ocular Lesions* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions

3 *Carcinoma* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives Close clinical surveillance of users is, nevertheless, essential In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropr ate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care

4 *Hepatic Tumors* Benign hepatic adenomas have been found to be associated with oral contraceptives Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time

5 *Usage in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring* During early pregnancy, female sex hormones may seriously damage the offspring

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy

6 *Gallbladder Disease* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives

7 *Carbohydrate and Lipid Metabolic Effects* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives

An increase in triglycerides and total phospholipids has been observed

8 *Elevated Blood Pressure* An increase in blood pressure has been reported in patients receiving oral contraceptives The prevalence in users increases with longer exposure Age is also strongly correlated with development of hypertension Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure

9 *Headache.* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives

10 *Bleeding Irregularities* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives In breakthrough bleeding, nonfunctional causes should be borne in mind In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives

11 *Ectopic Pregnancy* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures

12 *Breast-Feeding* Oral contraceptives may interfere with lactation Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs

PRECAUTIONS

1 A complete medical and family history should be taken prior to the initiation of oral contraceptives The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2 Preexisting uterine leiomyomata may increase in size

3 Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

4 Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated

5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice If jaundice develops, the medication should be discontinued

6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function

7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency

8 Serum folate levels may be depressed

9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted

10 Certain endocrine and liver function tests and blood components may be affected

(a) Increased sulfobromophthalein retention (b) Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone (d) Decreased pregnanediol excretion (e) Reduced response to metyrapone test

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives. thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related. nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma, breast changes, change in weight, change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates; vaginal candidiasis, change in corneal curvature, intolerance to contact lenses

The following adverse reactions have been reported and the association has been neither confirmed nor refuted premenstrual-like syndrome; cataracts, changes in libido; chorea, changes in appetite; cystitis-like syndrome, headache; nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum; hemorrhagic eruption, vaginitis; porphyria

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication

After several months on treatment, bleeding may be reduced to a point of virtual absence, reduced flow may be a result of medication and not indicative of pregnancy

HOW SUPPLIED

Norlestrin 21 1/50 is available in compacts each containing 21 tablets Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin 21 2 5/50 is available in compacts each containing 21 tablets. Each tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin Fe 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin FE 2 5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets Each pink tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin 28 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills

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North Carolina Medical Journal

Features for Patients September 1985

Accidental *Veratrum Viride* Poisoning in Three "Ramp" Foragers

Daniel Crummett, M.D., Deborah Bronstein, M.D., and
Zebulon Weaver, III, M.D.

"Ramps (*Allium tricoccum)* have become an increasingly popular seasonal delicacy in Southern Appalachia. With their distinctive onion/garlic flavor and odor it would seem difficult to mistake other plants for ramps. Unfortunately, however, other plant species are morphologically similar and might confuse the inexperienced ramp forager. In this report we describe three young adults who became seriously ill after ingesting what they thought were ramps.

Case Report

One man, D.G., and two women, S.R. and K.G., ages 30, 28 and 28 respectively, after reading a newspaper account of a local ramp festival, proceeded to the Blue Ridge Parkway to forage ramps. They had not previously eaten or identified the plant. Encouraged by a confident bystander the threesome picked approximately one dozen plants which they believed were ramps. Bulbs of the plants were removed and added to an egg salad which all three ate. Several hours after eating they presented to the emergency room with weakness, nausea, hypotension and bradycardia.

K.G. developed crampy abdominal pain with nausea approximately thirty minutes after ingestion and began self-induced vomiting. She presented to the emergency room with the following vital signs: pulse 58, respiratory rate 20 per minute, and blood pressure 94/60. The rest of the physical examination was unremarkable except for pronounced pallor. EKG was normal except for sinus bradycardia. Electrolytes were as follows: sodium 130, potassium 3.9, chloride 101, CO_2 30, anion gap -1. Blood pressure dropped to 80/52 and the heart rate to 55 after several hours in the emergency room. After four hours of observation the patient was asymptomatic and the blood pressure was 90/60; therefore, she was discharged home.

S.R. presented with the following vital signs: temperature 96.5, pulse 60, respirations 18 and blood pressure 80/50. Remarkable physical findings included pronounced pallor and a slight diffuse abdominal tenderness. EKG revealed sinus bradycardia with a rate of 51 and first degree heart block with a P-R interval of .31 seconds. Continuous monitoring revealed brief episodes of second degree atrioventricular heart block (Mobitz I). Electrolytes were as follows: sodium 132, potassium 4.4, chloride 108, CO_2 24, anion gap 0. Complete blood count and urinalysis were unremarkable. One liter of normal saline was infused over one hour and 10 ounces of magnesium citrate were given. Approximately four hours after admission the patient's P-R interval was .20 seconds, pulse 74 and blood pressure 90/50. She was admitted for cardiac monitoring and had an uneventful 24 hour course and was discharged. Electrolytes and anion gap on discharge were normal. The P-R interval returned to .17 with a heart rate of 74 and blood pressure of 100/62.

D.G. presented with the following vital signs: temperature 98.6, pulse 50, respirations 20, blood pressure 70/32. He was initally alert, but slow to respond. Remarkable physical findings included pronounced pallor and a grade II/IV systolic murmer (which was later shown to be secondary to bicuspid aortic valve by echocardiography). Twelve lead EKG revealed sinus bradycardia with a rate of 48 and peaked T waves in the anterolateral leads (13 mm height). Electrolytes were sodium 138, potassium 3.9, chloride 108, CO_2 27.8, anion gap 2. Complete blood count and urinalysis were unremarkable. Upon arrival at the emergency room one liter of lactated Ringer's solution was infused over twenty minutes and IM Compazine was given to control vomiting. Approximately one hour after arrival the patient's blood pressure became 60/20 prompting a continuous I.V. dopamine infusion at 2 mg/kg/min which quickly raised the blood pressure to 90/60. The patient's blood pressure remained stable after the discontinuation of dopamine. The heart rate, however, dropped to 46 on several occasions. At discharge the patient's electrolytes and anion gap were normal and the peaked T waves had resolved and were 5 mm in height.

Discussion

Several of the plants in question were retrieved in the emergency room. Although we were initially unable to identify the plants we were able to determine that they were not ramps. The possibility of digitalis toxicity from plant ingestion was strongly considered; however, this was questioned because the degree of hypotension seen would be unusual in digitalis toxicity. We felt that the degree of bradycardia could not explain the degree of hypotension. Also, Foxglove and Lily of the Valley (known digitalis-containing plants) were eliminated as possibilities because of morphological dissimilarities from the plants in question. It wasn't until several days later that we were able to correctly identify the plants as *Veratrum viride* (or more commonly False Hellebore).

Veratrum viride is a perennial herb which is widely distributed in wet or swampy ground throughout the northern hemisphere. The pharmacology of *Veratrum* is complex and contained within the plant are many toxic alkaloids. Glycosidic and ester derivatives of alkamine alkaloids have been identified, the latter of which are the principal hypotensive agents.[1]

Veratrum alkaloids produce hypotension and a concomitant bradycardia. Hypotension is independent of a change in heart rate. Reflex phenomena whose afferent vagal impulses are thought to arise in the carotid sinuses, left ventricle and lungs are thought to result in hypotension secondary to vasodilatation and bradycardia. Atropine will not completely abolish hypotension, but will prevent bradycardia; therefore, it appears that the vagi are the efferent arms of the reflex for the heart, but the efferent mechanism for hypotension is more complex.

Veratrum alkaloids also produce a direct depressant effect on respiration and a direct bronchoconstrictor effect. Vomiting is thought to result from a reflex involving the nodose ganglion.

After ingestion, *Veratrum* alkaloids usually act within two hours and effects may persist for four to six hours. They are degraded in the liver and excreted in the feces.[1,2]

Veratrum species have been used for medicinal purposes for hundreds of years. They were used in sorcery during the Middle Ages and in folk medicine as counter irritants in neuralgia, as cardiac tonics, as emetics and to treat fever. *Veratrum viride* was also employed as an American Indian potion to test the stamina of young Indian braves.[3,4]

In the early 1950s *Veratrum* alkaloids were among the first antihypertensive agents used in the United States. They have been used in the treatment of essential, renal, and malignant hypertension as well as in pregnancy-induced hypertension syndromes. With newer antihypertensive agents the *Veratrum* alkaloids fell into disfavor because of the narrow range between therapeutic and toxic doses.[3]

The cases presented certainly typify the effects of *Veratrum* alkaloid poisoning. Of note, however, are the peaked T waves of D.G. which resolved after an increase in heart rate and blood pressure. Also of interest are the initial decreased anion gaps

of all three patients. The reason for this is unclear but may represent laboratory error.

Veratrum viride and *Allium tricoccum* (or "ramps") are both found in southern Appalachia and have almost identical distribution patterns; however, there should be little difficulty differentiating between the two. The most obvious difference is the very strong odor of leeks which "ramps" possess, but which *Veratrum viride* lacks.

Morphologically, the two plants are dissimilar when mature; however, there are similarities during early spring when "ramps" are in season. *Veratrum viride* has deeply veined leaves originating from a stem. The mature plant is very leafy. The length to width ratio of leaves from a mature plant is 2.5/1 which is less than the length to width ratio of a young plant. The bulb of *Veratrum viride* is slender.

Allium tricoccum has only two leaves, which are smooth. Length to width ratio of leaves is 4-5/1. There is no stem and the bulb has a slightly fibrous coat.

Conclusion and Summary

As with all foraged foods, ramps must be carefully identified, preferably by an experienced person, prior to ingestion. Identification will be aided by the strong odor of leeks. Mistaken ingestion of *Veratrum viride* can have serious complications including first and second degree atrioventricular block, significant hypotension, respiratory depression and even death. With "ramps" gaining increasing popularity, western North Carolina physicians should be suspicious of accidental *Veratrum viride* poisoning in patients appearing toxic after the ingestion of "ramps."

We are indebted to Dr. Evans Whitaker and Dr. J. Lowell Orbison for their help in identifying *Veratrum viride*.

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Removing a Tick

Daniel L. Dolan, M.D. and John J. McKinsey, M.D.

Many methods of removing an embedded tick have been devised. Most have proved fallible. Such procedures as burning the tick's posterior with a recently lighted match head or cigarette so that the tick would voluntarily remove himself, painting the tick with noxious and assumed painful materials such as nail polish, etc., have met with only limited success. Quite often once these approaches fail, the tick is pulled off forcibly, occasionally with dislodgement of the head which remains in the wound. The following method has been reliable the majority of the time:

1. Squeeze 2% lidocaine jelly (available at most drug stores; 5% lidocaine ointment is faster, but requires a prescription) out of the tube so as to immerse the embedded tick.
2. Wait approximately 10 minutes.
3. Remove the tick with blunt forceps.

The mechanism employed by the tick to hold the head inside the skin seems to become anesthetized and flail. At this point the tick with its head may be easily removed.

In the Piedmont and western sections of North Carolina, the appearance of fever or any febrile illness 3-12 days following a tick bite should be promptly evaluated by a physician. If no clear-cut cause is found, empiric tetracycline therapy should be strongly considered since the diagnostic rash of Rocky Mountain Spotted Fever occasionally appears dangerously late in its course.

Lidocaine sprayed into the external auditory canal has been found to cause a cockroach to exit rapidly. Will wonders never cease![1]

Reference

1. O'Toole K et al. Removing cockroaches from the auditory canal: controlled trial. N Engl J Med 1985; 312:1197.

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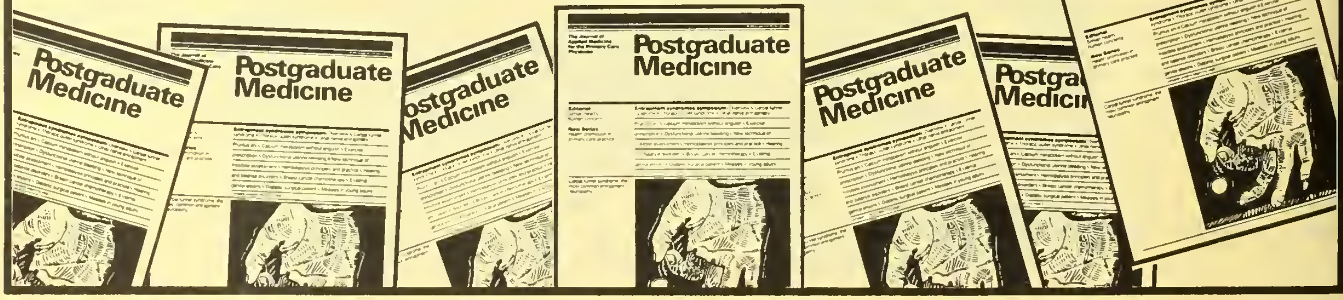

SCIENTIFIC ARTICLE

Sebaceous Gland Carcinoma of the Eyelid: Complete Response to Sequential Combination Chemotherapy

Barton R. Paschal, M.D. and Carter S. Bagley, M.D.

- *This is the first reported use of chemotherapy in sebaceous gland carcinoma of the eyelid.*

SEBACEOUS gland carcinoma (SGC) is a rare neoplasm occurring most often in older adults.[1] It is unfortunate that the vast majority of these tumors arise in the eyelid, caruncle or orbit because it is precisely when arising from these sites that SGC displays its most aggressive clinical behavior.[2, 3] The sebaceous gland most frequently involved is the eyelid gland of Meibom (Meibomian gland).[1] Wide excision of SGC of the eyelid is usually curative, but tumor-related mortality does occur.[2, 4] Radiation therapy appears to have a palliative role in the management of patients with unresectable SGC.[5] Heretofore, there have been no published accounts regarding the use of chemotherapy in this disease. Our report concerns a middle-aged man with locally advanced SGC of the eyelid who attained a complete response with sequential combination chemotherapy.

Case Report

In April 1979, a 48-year-old man was examined by an ophthalmologist for treatment of a small lesion on the lower left eyelid. When the lesion failed to respond to conservative measures, it was curetted. The nodule promptly recurred and a course of topical glucocorticoids was administered without success. In October 1979, the lesion was biopsied yielding a diagnosis of SGC.

The patient underwent two consecutive wide local excisions between October 1979 and June 1980. Subsequently, a discrepancy in the height of the globes was detected. In September 1981, a head CT scan revealed a mass along the inferior and medial wall of the left orbit. The next month, a left orbital exenteration with resection of the inferior and medial wall of the orbit and the left ethmoid sinus was performed.

In spite of these efforts, the patient suffered another recurrence 17 months later. The lesser and greater left sphenoid wing and lateral aspect of the left superior orbital fissure were resected in March 1983 to facilitate removal of a left orbital apex recurrence. At that time, the left temporalis muscle was advanced through the cranial defect and attached to the left orbital apex. The skin graft that was placed over this muscle flap was biopsied three months later and revealed SGC.

A course of radiotherapy to the involved orbit was completed in August 1983, but another graft recurrence appeared in April 1984. Intralesional 5-fluorouracil (5-FU) diminished the size of this recurrence, but when a biopsy of the left maxillary alveolar ridge disclosed SGC in June 1984, this therapy was discontinued and a head CT scan was obtained (figure 1A).

Next, the patient received four cycles of intravenous doxorubicin 25 mg/m^2/day for two days in conjunction with a 96-120 hr intravenous infusion of 5-FU 1 g/m^2/24 hr at three week intervals. Head CT scans obtained before and after the fourth cycle of therapy demonstrated no interval changes; however, in comparison with the baseline CT scan, substantial tumor regression had occurred (figure 1B).

In October 1984, a limited left maxillectomy with left maxillary sinus biopsies demonstrated residual disease. Afterwards, the patient received three courses of cisplatin 80 mg/m^2 and vinblastine 5 mg/m^2 intravenously between November and December 1984. Repeat left maxillary and nasal sinus biopsies in January and February 1985 were uniformly negative for malignancy. The patient remains clinically free of recurrent disease to date.

Discussion

A recent reduction in the mortality of patients with SGC of the eyelid has been attributed to wider recognition of the clinical and pathologic characteristics of this disease.[2] Meibomian gland carcinoma can masquerade as a chalazion or stye; therefore, a high index of suspicion is helpful in making a prompt diagnosis. The interval between onset of symptoms and diagnosis in this case was six months, which compares favorably to the mean interval of 1-2 years reported by others.[1, 2, 5]

When conventional therapy failed to control our patient's malignancy, a chemotherapeutic approach was entertained. To our knowledge, there are no previously published accounts regarding the use of chemotherapy in SGC. We patterned our patient's therapy after that used to treat unresectable adenoid cystic carcinoma of the salivary gland

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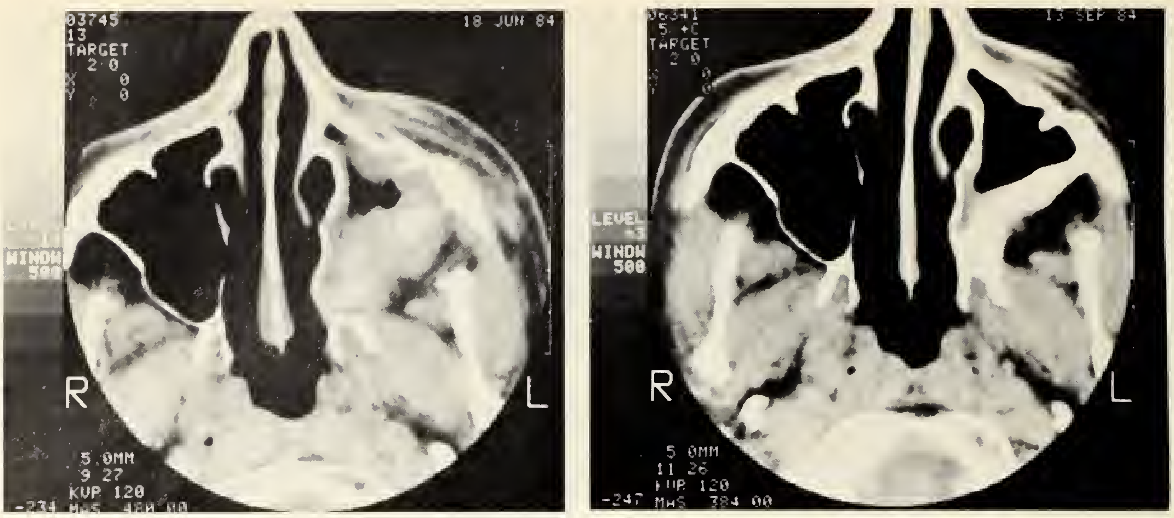

Figure 1. *CT scan of the head of our patient just before he started chemotherapy (left) and after the fourth cycle of chemotherapy (right). There was considerable regression of the tumor between the two scans.*

for the following reasons: 1) sebaceous neoplasms can arise from salivary glands; 2) adenoid cystic carcinoma sometimes displays sebaceous differentiation; and 3) the natural history of adenoid cystic carcinoma is similar in some respects to that of SGC.[4, 8]

Effective chemotherapy exists for patients with adenoid cystic carcinoma. Johnson et al. reported two patients with adenoid cystic carcinoma who responded to an intra-arterial infusion of 5-FU, one of whom ultimately achieved a complete response.[9] Doxorubicin has also shown activity in this disease.[10, 11] Accordingly, we chose to treat our patient with intravenous 5-FU and doxorubicin. Since 5-FU is more effective in patients with head and neck cancer if administered as a continuous intravenous infusion, we opted for this schedule.[12]

When a head CT scan obtained after the fourth cycle of 5-FU and doxorubicin showed that no further improvement had occurred, we reasoned that a fifth cycle was unlikely to be helpful if cure had not already been achieved. This line of thought stemmed from the collective experience of a number of clinical investigators who have utilized relatively brief durations of therapy to treat chemosensitive tumors without compromising cure rates.[13, 14, 15, 16] Furthermore, our patient had already received an additional course of chemotherapy after maximum tumor regression had been documented on the head CT scan obtained between the third and fourth cycle of chemotherapy. Finally, we hoped to avoid the emergence of a doubly resistant tumor clone by using a second potentially non-cross-resistant combination of drugs as soon as possible after maximum tumor regression had been achieved with the first combination (Goldie-Coldman hypothesis).[17]

The use of cisplatin and vinblastine (after doxorubicin and 5-FU had failed to effect a complete remission) was largely empirical. The complete response observed with cisplatin and vinblastine, after a partial response was obtained with doxorubicin and 5-FU, implies that these two combinations are non-cross-resistant. Although it is impossible to discern which drug(s) within each combination was (were) responsible for our patient's response, it is apparent that at least one drug within each combination was effective.

This case represents the first reported experience with chemotherapy in the treatment of SGC. After two sequential courses of combination chemotherapy were administered, our patient not only responded to each combination, but also achieved a complete response. We hope this report will stimulate interest in further defining the role of chemotherapy in the treatment of this disease.

Addendum

The patient recently experienced the onset of low back pain and lower extremity weakness. A myelogram shows extradural compression of the spinal cord in the midthoracic spine. Cytologic examination of the spinal fluid shows malignant cells. Although re-biopsy of the temporalis muscle graft is unremarkable, there is strong clinical suspicion of a local recurrence.

Acknowledgment

We are indebted to Theresa Miller for secretarial assistance in the preparation of the manuscript.

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Complete reference list available from the NCMJ editorial office.

SCIENTIFIC ARTICLE

Cardiac Surgery in Asheville: Review of 326 Consecutive Cases During 1983

Kent W. Salisbury, M.D.

• *The results of this one-year study compare favorably with the CASS study and the population is sicker, more symptomatic and less stable.*

THIS is a retrospective survey of the pre and post operative status of 326 consecutive patients treated by Asheville Cardiology Associates during 1983.

Asheville, North Carolina is a city of approximately 60,000 people which serves as a referral center for cardiac catheterization and cardiac surgery for patients of western North Carolina. Geographically it is relatively remote.

Travel to the next closest catheterization and surgical center in the state takes 2½ hours. The medical and referral population of Asheville is approximately 400,000 individuals.

As a rural population the patient mix is predominantly blue collar with an enlarging percentage of retired citizens as the popularity of rural western North Carolina increases. The elderly Medicare population comprises approximately 35% of hospitalizations at Memorial Mission Hospital, one of two general hospitals in Asheville.

The cardiology services program has steadily expanded over the past decade, and for several years has had enough patients to meet the recommended national standards for centers for catheterization and cardiac surgery. Cardiology services are provided by the six board-certified cardiologists of Asheville Cardiology Associates and surgical services by a single cardiovascular surgery group of five board-certified cardiac surgeons.

To avoid fragmentation of services and to maintain quality and cost effectiveness, the medical staffs and administrations of St. Joseph's and Memorial Mission Hospitals have agreed to perform all invasive cardiology evaluation and cardiac surgery for the patients of both hospitals at Memorial Mission Hospital. Both hospitals provide noninvasive cardiology services.

For the purpose of this survey the following terms are defined:

1. Elective Surgery: Surgery performed on electively scheduled admission to hospital (145 patients — 44%).
2. Urgent Surgery: Surgery performed during the same hospitalization as catheterization generally because of instability, the patient being considered in a high-risk subset (eg, significant left main coronary stenosis), or because of refractory symptoms or signs (164 patients — 50%).
3. Emergency Surgery: Surgery performed on an emergency basis within hours of consultation because of acute and uncontrollable decompensation (17 patients — 5%).
4. Ventricular Dysfunction:
    a. Normal: Ejection fraction (EF) >50% and no wall-motion abnormalities in RAO projection.
    b. Mild: EF >50% with minor hypokinetic segments.
    c. Moderate: EF >25-50% with significant wall-motion abnormalities.
    d. Severe: EF <25% with marked wall-motion abnormalities.

Valve Surgery

Of the 326 cardiac patients 30 required valve surgery alone, 12 urgently. There were 14 mitral procedures (replacements plus open valvulotomies), ten aortic valve replacements and six combined mitral and aortic replacements. Fifteen additional patients who had valve surgery also had coronary bypass grafts (ten were urgent or emergent). Seven patients required one coronary vein bypass graft (CABG) (five mitrals, one aortic and one aortic + mitral); four required two grafts (two mitrals and two aortics); one required three grafts (mitral); two required four grafts (two mitrals) and one required five grafts (mitral). The patients who required three or more grafts had mitral valve replacement because of mitral complications of coronary disease.

Of these 45 patients undergoing valve surgery, four required emergency surgery for acute hemodynamic compromise (one aortic and three mitral). Eighteen patients required surgery urgently because of intractable Class IV symptoms, refractory congestive heart failure or unresolved sepsis with endocarditis (ten mitrals, three aortics and five mitral + aortic). The remaining 23 patients underwent elective surgery (12 mitral, nine aortic and two mitral + aortic).

There were no deaths in the elective surgery group.

There were four early deaths in the urgent group (two mitral and two aortic). Three of these patients had significant left ventricular dysfunction and one had had recent septic shock with hypotension and severe acute mitral insufficiency from papillary muscle infarction. All four of these deaths had concomitant coronary bypass grafts.

There was no early mortality in the emergency surgical group.

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Overall early mortality for valve surgery was therefore four of 45 cases or 8.8% (2/25 mitrals, 2/13 aortics — all requiring CABG).

Nonvalve-Noncoronary Surgery

Seven patients underwent correction of atrial septal defects. One had ligation of a patent ductus arteriosus. There was no mortality in this group. One patient died who underwent attempted emergency pulmonary embolectomy for refractory shock following saddle embolization.

Coronary Bypass Surgery

Coronary artery bypass surgery was performed on 288 patients. As mentioned above, 15 had concomitant valve surgery leaving 273 with only CABG. Of the 288 patients there were 64 women (22.2%) with an average age of 64.6 years. There were 224 men (77.8%) with an average age of 58.6 yaars.

In the CABG group there were 13 early deaths for an operative mortality of 4.5%. However, if one excludes valve replacement combined with CABG the mortality decreases to 9/273 or 3.2%. If emergency operations are excluded, the mortality is 6/257 or 2.3%. Excluding urgent operations the mortality falls to 2/119 or 1.7%.

As in many published studies the risks of cardiac surgery in our center increase with the severity of coronary artery disease, the severity of left ventricular dysfunction, age and sex of the patient and to a certain extent with non-specific preoperative risk factors. The number of grafts placed in this patient population (mean 3.8) defines this group as one with more severe atherosclerosis than in the CASS randomized group (mean 2.7)[1] or in other published studies.

Thirty-three percent of our patients were hypertensive, 45% were current or recent smokers and 10% were diabetic. Of the 16 patients who had both diabetes and significant hypertension there were three deaths for a mortality of 18.7%. Patients with diabetes but no hypertension or smoking had no mortality. Likewise, there were no deaths in the patients with diabetes who smoked but were not hypertensive.

Seventeen percent (49 patients) had had acute myocardial infarction within four weeks of surgery. There was no mortality at surgery if there were no additional risk factors.

Old myocardial infarction was present in 36% (104 patients). Unstable angina was present in 38% (110 patients). Eighteen percent of our patients (53 patients) had both unstable angina and old infarction. There were eight early deaths in this group (15% mortality).

Forty patients (13.9%) had congestive failure; four (10%) had early mortality.

Therefore in this series the hypertensive diabetic patient and the patient with unstable angina superimposed upon prior myocardial infarction were at significant risk. Congestive heart failure also increased risk.

There were 23 (10.7%) men over age 70, 40 (18.6%) between 65 and 70 and 152 (70.7%) under 65. Of 62 women, there were 12 (19.3%) over 70, 14 (22.6%) between 65 and 70, and 36 (58.1%) under 65.

When one looks at early mortality as a function of sex and age, there were three deaths in the male group (1.4%) and six deaths in the female group (9.7%). There was one death in a man over 70 (4.3%), one death in the 65-70 male group (2.5%) and one death in the group under 65 (1.2%). In the female group there were two early deaths among the 12 patients over 70 (14.2%), three in the 65-70 group (22.2%), and one in the group younger than 65 (2.8%).

In terms of left ventricular function the early deaths occurred once among 80 normal ventricles (1.2%), four times in 93 patients with mild LV dysfunction (4.3%), twice in 62 patients with moderate dysfunction (3.2%), and twice in 27 patients with severe dysfunction (7.4%). In 15 cases ventricular function was not listed.

Attesting to the severity of illness among the nine CABG patients who had early death was an average graft number of 4.7, refractory and continuing unstable angina in all nine patients, prior myocardial infarction in eight and an average age of 67 years.

Considering mortality in relation to urgency of surgery in our entire series (valves, CABG and combined) there were 14 early deaths (4.3%). Of these, four occurred among 17 emergency cases (24%). One was a pulmonary embolectomy, one double bypass with normal LV function and two multiple CABG with severe LV dysfunction.

Of the 164 patients requiring urgent operation, there were eight early deaths (4.9%). In this group there were two mitral valve replacements with CABG for severe mitral insufficiency secondary to coronary disease, two aortic valve replacements and CABG for significant aortic insufficiency and coronary disease and four patients with more than three CABG, all over age 60 (three women).

Finally, among the 145 patients undergoing elective surgery there were two early deaths (1.3%). Both were women (aged 69 and 71) and each had five CABG.

Preoperative NYHA functional classification of our surgical series identifies this group as a highly symptomatic and incapacited population. With complete revascularization virtually all our CABG patients returned to Class I. Of the patients under age 65, 154 were actively employed, a high rehabilitation rate. Patients who returned to work tended to have had symptoms for a shorter period of time (days to months) than did those who did not (months to years).

Morbidity of Cardiac Surgery

Morbidity in cardiac surgery is significant even if a

Table 1
Cardiovascular and Pulmonary Morbidity

Respiratory failure	10
Atrial arrhythmias	29
Ventricular arrhythmias	10
Excessive bleeding	10
Tamponade	3
Reoperation	7
Intraaortic balloon pump	9
Myocardial infarction	6
Pericarditis	20
Infection	10
Stroke	3
Permanent pacemaker	3
Pulmonary embolus	4
Congestive failure	3
Peripheral vascular comp.	3

Table 2

Noncardiac Morbidity in 12/311 Survivors

Rash	1
Pancreatitis	2
Sternal separation	1
Paretic diaphragm	1
Renal failure	1
GI bleeding	1
Bypass graft occlusion	1
Brachial plexus injury	1
Pneumothorax	1
Tracheostomy	1
Prostatectomy	1

center has "acceptable" mortality statistics.

Among the 311 survivors in the entire series, 80 (25.7%) had either major or minor morbidity as summarized in table 1. Table 2 details miscellaneous and infection morbidity. Twenty-one patients had only one morbid event (6.6%). Thirty-two had two events (10.1%). Sixteen had three events (5.1%) and 11 had more than three (3.5%).

Not surprisingly, sepsis, renal failure and hemodynamic failure were more prevalent in the 15 patients who died. Multiple morbid events (greater than three) occurred in five of these patients (35.7%).

Discussion

This study is a retrospective review of a relatively small number of cases and as such is subject to sampling errors and bias. However, the study was initiated as an attempt to compare our surgical results with published statistics, and to survey the quality of our program in the light of other reports.

The study was also performed to compare our patient population to the widely-publicized CASS randomized study[1] and to provide information to those who would assert that "unnecessary" coronary bypass surgery is being performed.

The CASS randomized study had restrictive entry criteria which included: 1. angiographically documented 70% occlusive coronary disease of the proximal or middle portion of at least one coronary artery; 2. age less than 65 years; 3. minimal or absent angina pectoris as defined by the Canadian Cardiovascular Society (a modification of the New York Heart Association classification); 4. an ejection fraction of >35% on angiography. More importantly, the study excluded patients who had left main coronary stenosis; who were older than 65 years; who had moderate or severe angina; who had distal coronary stenosis; who had ejection fractions <35%; who had ventricular aneurysms; who were likely to require mitral valve replacement along with CABG; who had inoperable vessels, prior CABG or congestive heart failure; who had coexistent illness which would increase the likelihood of death within five years; and who for various other reasons could not participate in the study (geographic restrictions, etc.). Of course patients with normal coronary arteries and those who had not undergone angiography were also excluded.

The operative mortality in the CASS randomized patients was 1.4%. In our own series the patients undergoing elective coronary bypass surgery carry a comparable mortality of 1.7%. Our practice has always been to medically treat the patient with characteristics similar to the CASS randomized patients. Our surgical population is therefore a more symptomatic, less stable group. Yet it still compares favorably in surgical mortality.

Generally the composition of this series compares favorably with large surgical series in preoperative characteristics such as age, sex, smoking, diabetes, prior myocardial infarction, symptoms and coronary anatomy. However, there are important differences in direct comparison with any single series. For example, in the CASS registry as reported by Kennedy et al,[2] urgent or emergency surgery comprised 19.4% of the study population. In our own series these groups contained 181 patients or 55.5% of our series. Our definition of urgent or emergent is identical to CASS. The community hospital may be exposed to a sicker population of patients who cannot be transported to major referral centers.

The overall mortality in our surgical series of 326 patients is 4.25% and the series is weighted toward the unstable and critically ill patient. If one compares urgent and emergency CABG with the CASS urgent and emergency cases, our mortality of 7/176 or 3.9% is identical.[1] Considering the large percentage of urgent and emergent cases in the remainder of the series (48.9) our mortality experience also is "acceptable" in comparison with other similar series.[3] Educational efforts to encourage earlier referral of valve and CABG patients are underway.

Of interest and concern in our study is the high mortality in the hypertensive-diabetic patients. Although each of these risks has been identified to be associated with increased operative mortality, other studies suggest no increase in operative mortality in these and that the apparent increase is in fact related to other variables.

The number of deaths in our series was small. The patients who died had other well-recognized risks than diabetes and hypertension, including old myocardial infarction, unstable angina, older age, female sex and multivessel disease necessitating placing an average of 4.7 grafts. It is difficult in this small series to implicate diabetes or hypertension per se. However, in looking at the historical features of diabetes, hypertension, unstable angina, old myocardial infarction and left ventricular dysfunction, it is apparent that the challenge of adequate myocardial preservation is greatest in these patients.

The bias in our surgical program has been toward complete vascularization. The higher number of average grafts in our series probably attests to this practice, as does the excellent improvement in postoperative functional capacity that we have demonstrated. It is interesting that some investigators suggest there may be a diminished need for coronary reoperation in those patients who have had "complete" revascularization at the first operation. Our center has seen relatively few candidates for reoperation thus far, but I have no data to show that this is the result of complete revascularization.

As in other published series, women in our series had a higher mortality than men for CABG. It is interesting that in the CASS registry, the increased risk in young women compared with men disappears in the elderly population.

The female patients in our series being comparable to other published subsets, it seems likely that the high mortality in women in our small series is the result of chance or of other concurrent risks such as age, ventricular dysfunction, unstable angina, etc.

Morbidity and postoperative rehabilitation are also important criteria for judging a program's quality. The recent study by Kuan et al[4] summarized CABG morbidity in a surgical series comparable in size to our own. The incidence and type of major and minor complications in our two series were similar. Our patients required intra-aortic balloon pump insertion more frequently (nine cases compared with two cases) and additional complications of pancreatitis (two cases), brachial plexus injury (one case), pleural empyema (one case) and non-A non-B hepatitis (two cases) were noted. There seemed to be a higher incidence of respiratory distress syndrome (13 cases or 4%) in our series compared with none in the Kuan series and 1.6-1.8% in a Cleveland Clinic Series.[5] The incidence of minor complications such as pericarditis, atrial fibrillation, cellulitis and phrenic nerve palsy were very similar in the Kuan series and in ours (3.2%). The subsets of these patients have already been discussed. In their series and ours the major morbidities of renal failure, heart failure, shock and sepsis were prevalent among the patients who died.

Finally, 82% of our CABG patients under 65 years of age returned to work following their surgical convalescence. Considering that this group is weighted toward a blue collar population this is a larger percentage than reported by some studies, but similar to others. The shorter duration of symptoms in the group that returned to work attests to the benefit of early CABG in the significantly symptomatic patient in achieving full rehabilitation. Care in the patient's own community or region causes less social disruption and may also facilitate rehabilitation.

The Editor thought the author's summary was too long and repeated the substance of his article. The Editor's summary is: "If you live in western North Carolina and need cardiac surgery, you are well off."

Acknowledgment

I wish to thank Mr. William Lang, Physician's Assistant for Asheville Cardiology Associates, P.A. as well as Ms. Ann Welborn and Ms. Denise Hughes, R.N. for Drs. Keller, Mauney, Claxton, Bilbrey, Burton and Associates, P.A. for their valuable assistance in reviewing and abstracting records.

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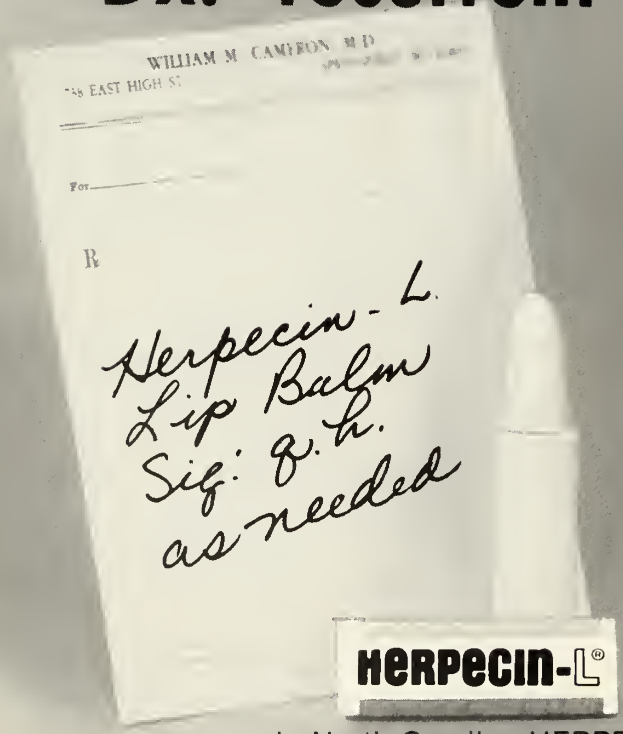

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SCIENTIFIC ARTICLE

Cancer Immunology Is a Rapidly Developing Field

Warren H. Cole, M.D.

• *An overview of cancer immunology today.*

WE know many of the agents that can produce tumors and are beginning to understand how they alter cells to make them immortal. Tumor cells carry surface markers not present on normal cells. These tumor markers act as antigens and activate the immune system.[1] Many tumors metastasize, and we are beginning to understand how the body mobilizes its forces to resist metastasis. The role of the immunologic system in resisting bacterial and viral infections is well known to us.[2] This paper summarizes the evidence that this familiar immunological defense system is used to destroy wandering cancer cells. A weakened defense system, be it the result of hereditary defects, immunosuppressive drugs, poor nutrition, operative trauma, infections with virus or bacteria or changes in mood, can alter the immune system and make metastases more likely.

I will not describe the role of macrophages, the several types of lymphocytes, the immunoglobulins and other features of the immune system. This information is readily available in the recent literature.[2-4] I will stress that the immune system is a dynamic and very changing system. Tumors under favorable conditions mobilize the immune system for effective action.[1] Many environmental changes depress the immune system and alter the balance in favor of the tumor.[5-9]

Each day the number of known tumor-specific antigens to which the body develops antibodies increases. The tumor cells are not inert, and they may develop substances that may result in non-specific suppression of the patient's immune system. Surgery itself may set the stage for an effective immune reaction.[1] For example, when the tumor is excised, the host's immune system may then be able to destroy a moderate number of tumor cells encountered in early metastasis.

Unfortunately, the trauma of anesthesia and surgery may in itself cause immunosuppression.[10,11] Evidence of surgical immunosuppression was first described in 1957. In this experiment 164 rats were divided into two groups. The control group of 79 rats had inoculation of 25,000 Walker cells subcutaneously. The 85 rats in the other group had an inoculation of 25,000 Walker cells subcutaneously plus a celiotomy during which the intestines were stirred gently (simulating a resection of a tumor). The "take" in the control group was 31.6% compared with 61.1% in the experimental group.[12] We did not test human beings to see if the immune resistance was damaged by a major operation because at that date we had no lymphocyte count tests, etc., available to be used as a test for immune status.

A knowledge of the role of the immune system in destroying tumor cells has cleared up the mystery of why radiation and chemotherapy can cure the original cancer but induce the development of other cancers. The agents destroying the cancer cells may alter other cells in a way that makes them cancerous and may have depressed the immune system to such a degree that the newly created cancer cells are not destroyed.

The concept that clones of malignant cells are constantly arising and that the body is constantly destroying them is an important one. It allows us to predict that whenever the immune system is impaired by a wide variety of causes, an increased incidence of cancer would be found. All series of major organ transplants that require immunosuppression have shown an increased incidence of a variety of cancers.[13-17] These include transplantation of kidneys, hearts and bone marrow.

Each month more evidence is presented about the many factors that alter the immune system. In recent months, evidence that the nervous system can alter the system has been presented.[18-21] We do not yet know the degree of immunosuppression that may occur in each of our lives as a function of the way we live. The need for immune protection against tumor cells must fluctuate. Many stimuli must affect the way that tumor cells migrate. What is effective immunity one day may be ineffective on another.

It is of interest that the genetic and acquired deficiency states characterized by altered immunoglobulins do not lead to the same incidence of cancer as do immunodepressive drugs. These disturbances in immunoglobulins do lead to severe and repeated infections. The physician caring for such patients should carefully examine changes in the host that permit bacteria, viruses and protozoa to flourish.

Modulation of the immune system by the brain is a rapidly developing area of knowledge. We are reproducing the preface of the book listed as reference 21 to encourage you to watch for developments in this area. Remember Eugene Stead's short summary of clinical medicine — "Never underestimate the nervous system."

Preface*

This is a time when advances in biochemistry and physiology permit us to consider, in experimental terms, the role of the central nervous system (CNS) in modulating the behavior of the immune system. The existence of such regulation should not come as a surprise, given the general role of the CNS in coordinating all systems of the organism. However, the nature, scope, and limits of the regulation

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* Reprinted with permission from *Neural Modulation of Immunity*, New York, Raven Press, 1985.

are far from being well understood. What is known is the subject of this book.

Neural Modulation of Immunity *is therefore addressed to those interested in the foundations of a rationale for psychological and pharmacological attempts to modulate immune responsiveness and, therefore, to a wide range of basic and clinical investigators as well as therapists and physicians who want an up-to-date survey of the empirical and conceptual state of the burgeoning field of psychoneuroimmunology.*

This is only the second book devoted entirely to the new field (aside from Mind and Immunity: Behavioral Immunology, *the annotated bibliography edited by S. E. Locke and M. Hornig-Rohan). In the three years since the publication of the first such book,* Psychoneuroimmunology, *edited by our contributor Dr. Robert Ader, several new aspects of neuroimmunomodulation have been increasingly studied and are covered only in this book – for example, the relationship of hemispheric laterality to immunity, and the innervation of the thymus gland and other lymphoid tissues.*

Before commenting further on the contents of this book, we wish to distinguish its main subject from three other important aspects of the relationships between the nervous system and the immune system.

First, this book is not about autoimmune disease of the nervous system. Second, it is not about the use of antibodies to neuronal and glial antigens in order to analyze the ontogeny or circuitry of the nervous system. Third, it is not about resemblances in function or analogies between the two systems, which are often described with similar terms, e.g., memory, recognition, learning, redundancy, diversity, etc.

This book is about the mechanism and role of regulatory communication between the central nervous and immune systems. The book opens with a tutorial analysis of the essence of intrinsic immune regulation. Subsequent chapters work their way from psychological through neuroanatomical to molecular levels of analysis. Several concluding chapters deal with conceptualizing nervous-immune system relationships. Most of the chapters are reviewd by active investigators in the field of work in their laboratories. The chapters are updated versions of presentations made at a conference held in Brussels in October, 1983.

The principles of these studies are straightforward: We look for regulatory connections between the CNS and the immune system that are coupled with relevant feedback from connections between the immune and nervous systems. Feedback is required because a regulator must monitor its own effect. The connectivity we seek must be both CNS-regulated and physiologically meaningful. It can involve messenger molecules or direct innervation affecting the ontogeny and responsiveness of the immune response.

The problem becomes ambiguous, but not less important, when we substitute "mind" for "central nervous system." The reason derives from the enormous differences between our understanding of "mind" and the immune system. No one would measure the velocity of an airplane by determining elapsed time with an atomic clock and traversed distance by dead reckoning. Yet we are forced to do something like this when we study the relationship between the immune system (dependent variable) and "mind" (independent variable). The immune system is understood in sufficient detail to measure the limiting factors in responsiveness with precision, while "mind" is a collection of subjective and objective events and processes: i.e., emotions, stress, cognition (conscious and unconscious), conditioning, volition, etc. This disparity would be sufficient reason to treat the problem circumspectly were not the effects of "mind" on immune reactivity so dramatic and paradoxical that the urge to understand becomes irresistible. This, unfortunately, encourages the use of anecdotal and correlative data to support a conclusion. Yet, quite often, the most fundamental and generalizable of concepts in biology begins with such a tolerated ambiguity which, in time, becomes delineated with experimentation. In view of the medical and social importance of "mind-related" effects on immune responsiveness, as well as our scientific curiosity concerning them, it is appropriate that we should undertake an analysis of the relationship by attempting to at least delineate the problem. This collection of essays is a modest step in that direction.

Roger Guillemin
Melvin Cohn
Theodore Melnechuk

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SCIENTIFIC ARTICLE

Fine-Needle Aspiration — An Aid to Breast Diagnosis

Peter A. Gentling, M.D.

• *Results of fine-needle aspiration of breast lumps and masses.*

THE breast is a particularly difficult organ to examine. To have a secure diagnostic understanding of benign versus malignant disease involves a combination of factors. The only way to assure the patient that she has no cancer in the breasts is to remove them and submit all the tissue to detailed pathologic analysis. Needless to say, bilateral prophylactic mastectomies are not practical and are certainly not desirable. Therefore we must rely on all diagnosic modes to help us detect the cancers that are so very frequent in the breast. We must try to find them as early as possible while looking toward preserving non-malignant breast tissue and avoiding costly and multilating biopsies where possible.

The history and careful physical examination are still the most important features in breast diagnosis. Various other means have been added to sharpen diagnostic acumen and to aid in earlier diagnosis. Mammography remains the basic aid, but recently an older approach has been revived. This involves cytologic evaluation of any area in the breast which feels peculiar and which the examiner is inclined to call abnormal. Fine-needle aspiration for cytology has the advantage of adding another diagnostic aid short of excisional biopsy. It has advantages in several ways. There are also some drawbacks to its use.

The technique for fine-needle aspiration was developed by Martin and Ellis and presented in a paper published in 1930.[1] Soderstrom[2] pointed out that the technique was not meant to replace conventional biopsy but to complement it. Interest in the procedure waned but was revived by the Scandinavians in the 1950s.

The advantages of fine-needle aspiration (FNA) include its cheapness, its accuracy when positive, the additional information it provides in lesions not suspicious enough for excisional biopsy and in lesions suspicious for cancer where a positive diagnosis would aid in setting up staging tests and patient-education discussions. Patients may also be reassured to know a negative cell study has been done. In those having previous breast cancer the remaining breast tissue is always suspect for another cancer. Vague thickened areas may not require biopsy but bear observation. Cell studies aid in these decisions.

Disadvantages of FNA include mainly sampling error. False negative tests may be common. Pain, hematoma and ecchymosis do occur but are minor. Cost of the procedure varies from $50 to $100.

The technique of FNA is easily learned. Equipment for its use is readily available and is inexpensive, but there is a technique that will maximize cell retrieval. If the procedure is poorly done, acellular specimens will result, yielding unreliable results. Some examiners use a special suction "gun" which holds the syringe, but normally-facile people do not need this special apparatus. A 10 cc syringe is used, attached to a #21 needle. No anesthesia is injected. The patient is supine with her arm held above her head to flatten the breast. The tissue in question is firmly trapped against the chest wall by three fingers of the operator's non-dominant hand. Needle introduction following alcohol swabbing of skin is accompanied by a warning that "now you will feel a small stick." The needle is passed in and out of the lesion while suction is maintained on the barrel of the syringe. Once tissue-fluid is seen in the needle neck, an adequate cell specimen is present in the needle. The instrument is withdrawn without suction so that air is not sucked up, pulling the cells into the body of the syringe. Two glass microscope slides are prepared using a drop of albumin as a protein fixative. The contents of the needle are squirted forcibly into this albumin. Occasionally a core of tissue can be removed in this way, but if little material comes forth, the albumin drop can be aspirated into the needle bore and expelled onto the slide. The two slides are touched gently together to spread the aspirate and placed directly in a container of 95% ethanol. Processing by the pathologist can follow immediately.

We make a practice of using the same pathologist for all our specimens since there is a knack of reading these slides and consistency is important. Any agreed-upon classification is acceptable. We have used a Class I through Class V approach. Class I and II smears are considered benign, Class III is suspicious, and Class IV and V are highly suspicious and frankly malignant, respectively.

False negatives remain a problem. Generally cancers will shed cells readily. When smeared, the slides are held to light; the albumin will be cloudy with cellular material. However, operator error in aspirating the proper tissue or getting considerable blood or cystic fluid can dilute the specimen and obscure malignant cells. Knowing when there is a good specimen is a matter of experience and is not difficult to learn, but a negative result is not necessarily a sign of benign disease. This must be constantly kept in

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mind. On the other hand, a Class IV or V smear has never been benign on subsequent biopsy in our experience, and under certain conditions, mastectomy has been performed with no more evidence than a suspicious physical examination, a condemning mammogram and a Class IV or V FNA.

The precise location of FNA is recorded on a patient breast consultation sheet with a clear diagram. Comments are recorded about grittiness of tissue, cellularity, associated bleeding — all signs of presumptive malignancy — and the presence of fluid with the disappearance of the mass with aspiration, relative acellularity, and softness of the mass — all signs suggesting the lesion is benign.

In terms of time, much can be gained by the FNA. At least an hour and a half is required in our office to discuss cancer of the breast, its treatment and implications. Much of this must be done prior to any operative diagnosis such as biopsy. In a busy office practice such discussion periods with the patient and her distraught relatives can needlessly frighten them while crippling an appointment schedule. Therefore, while negative FNAs do not make a benign diagnosis, they help, and positive FNAs allow for better allotment of office time to instruct the patient and her family. In addition, a bone-scan, chest x-ray and SMA-12 cost in excess of $200 and a half-day of the patient's time. These can be more appropriately ordered using a positive FNA and strong clinical suspicion. Our pathologists can give an answer to our FNA in two hours if taken early in the day. The patient is anxious for this news and grateful for any information.

During a three year period a total of 174 FNAs were performed. Of these, 35 (20.1%) were suspicious clinically and 139 (79.9%) were benign clinically. Table 1 shows the results. Although all lesions clinically suspicious were biopsied (as should be done), those considered benign clinically and biopsied showed a surprise malignancy rate of 2.2% and represented lesions that might not have been biopsied otherwise. The remaining 80 cases not biopsied were followed by return office visits and/or repeat mammograms. The cost-benefit per unsuspected cancer showed an expenditure of $1,475 for those cancers that might not otherwise have been biopsied. We consider this cost justifiable. There were no complications in our FNA series, and all were easily tolerated by the patients without the use of local anesthesia.

Table 1

Results of Fine-Needle Aspiration

Suspicious clinically		**FNA Benign**	**FNA Malignant**
Class I	0	0	0
Class II	3	0	3
Class III	15	0	15
Class IV	11	0	10*
Class V	6	0	6
	35	0	34
Benign clinically		**FNA Benign**	**FNA Malignant**
Class I	119	39†	0
Class II	16	12‡	0
Class III	2	1	1
Class IV	2	0	2
Class V	0	0	0
	139	13	3

*One patient, a 91-year-old woman, refused biopsy
†80 patients were not biopsied.
‡4 patients were not biopsied.

We believe fine needle aspiration to be a reasonable adjunct to breast diagnosis which can be utilized by all clinicians dealing with breast disease. The technique is easily learned, readily available, and not very expensive. It is safe and comfortable and adds another minimally invasive mode of diagnosis. One must keep in mind the occasional false-negatives (none in our series) so that an excisional biopsy can be done if a question arises such as in any solid dominant lump. Falsely positive findings are not a problem.

The benefits of the test include reassurance for the patient as well as the physician. They involve the more appropriate use of time in counseling patients in a busy office practice setting as well as helping to minimize the distressing discussion of malignancy and its treatment choices in those with benign disease. Occasionally FNA aids in finding malignancy early in the course of this enigmatic process.

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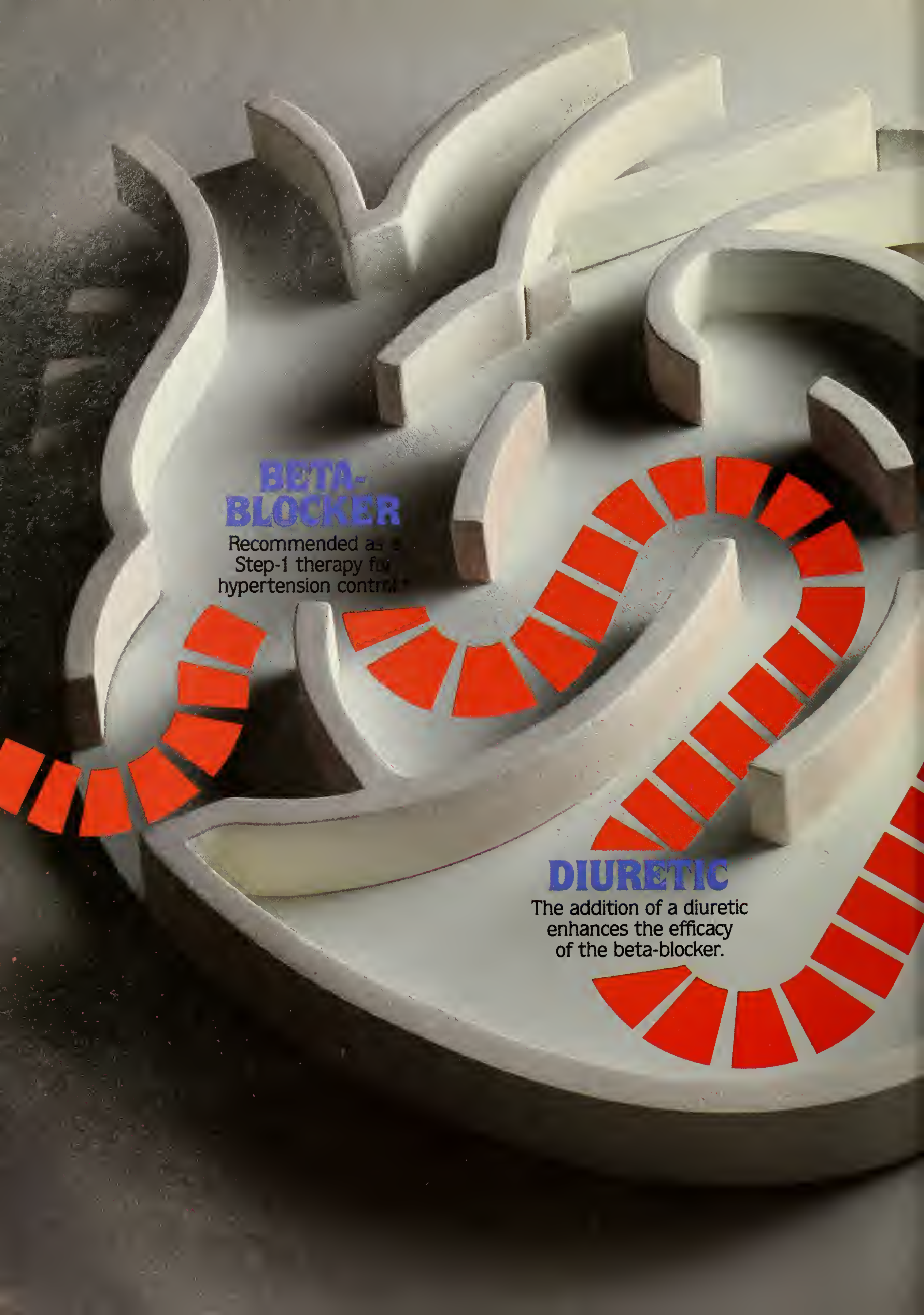
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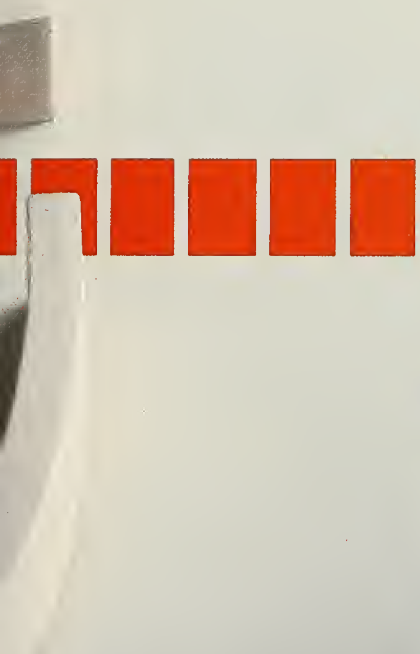

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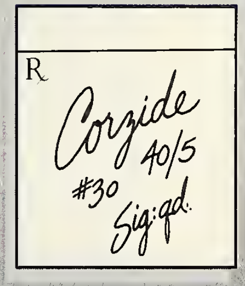

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*Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: The 1984 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 144:1045-1057, 1984.

Please see brief summary of prescribing information on following page

CORZIDE®

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CORZIDE® 40/5
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Nadolol-Bendroflumethiazide Tablets

DESCRIPTION: CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration combines two antihypertensive agents: CORGARD® (nadolol), a nonselective beta-adrenergic blocking agent, and NATURETIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations: 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide.

CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). **Bendroflumethiazide** — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS: Nadolol — Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — Nadolol — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and G.I. disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary arter insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, *Bendroflumethiazide*, and PRECAUTIONS, *General, Bendroflumethiazide).*

Drug Interactions — **Nadolol** — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents. **Anesthetics, general** — exaggeration o anesthetic-induced hypotension (see WARNINGS, *Nadolol, Major Surgery).* **Antidiabetic drugs (oral agents and insulin)** — hypoglycemia or hyperglycemia, adjust antidiabetic drug dosage accordingly (see WARNINGS, *Nadolol, Diabetes and Hypoglycemia).* **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect; monitor closely for evidence of hypotension and/or excessive bradycardia.

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics: **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of antidiabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or peripheral adrenergic blocking drugs** — potentiated effect. **Preanesthetic and anesthetic agents** — effects may be potentiated; adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, *General, Bendroflumethiazide).*

Carcinogenesis, Mutagenesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed.

Pregnancy — Teratogenic Effects — Nadolol — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose, no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus; these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash, pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling, weight gain; slurred speech; cough; nasal stuffiness; sweating, tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol. The following adverse reactions may also occur: **Central Nervous System** — reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss; emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia, Peyronie's disease; erythematous rash; arterial insufficiency.

Bendroflumethiazide — Gastrointestinal System — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersensitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed. Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, employ the following measures, as appropriate. **Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation. **Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a beta$_2$-stimulating agent and/or a theophylline derivative. **Stupor or Coma** — Supportive therapy as warranted. **Gastrointestinal Effects** — Symptomatic treatment as needed. **BUN and/or Serum Electrolyte Abnormalities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval, see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

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A Cost-Effective Community Model for Treating Alcohol Withdrawal Syndrome: A Preliminary Report

J. Paul Martin, M.D., Ellis Edney, Dan I. Gerber, Ph.D.,
William Meagher, David Silver, M.D.

- *An early report on a nonmedical detoxification center treating alcohol withdrawal syndrome since September 1984.*

THE alcohol withdrawal syndrome has been defined as the constellation of signs and symptoms that occur within hours to days of abstinence following habitual drinking of ethanol. The withdrawal syndrome may include anxiety, depression, tremor, tachycardia, hypertension, hallucinosis, confusion, seizures, or delerium tremens.[1-3] Because of the reported high incidence of morbidity and mortality associated with DTs, the traditional medical approach to acute detoxification of the alcoholic has included hospitalization, IV therapy and tapering doses of benzodiazepines. This approach is expensive, disruptive to the routines of a typical medical ward or ICU, and has not been shown to eliminate the mortality associated with delirium tremens. Additionally the high incidence of readmission for detoxification within weeks to months has been a source of frustration for medical house officers over the decades.

Nonmedical social setting detoxification has been promoted as a safe, cost efficient approach to the alcohol withdrawal syndrome. This concept was developed in 1969 by the Addiction Research Foundation in Toronto, Canada in response to observations of Canadian medical detoxification programs. N. William Petersen reported that 95% of the 4,000 patients seen over a 26-month period in a traditional medical detoxification facility did not require immediate medical care to become sober.[4] Instead, after designing and operating a social-setting detoxification model in Toronto, the experience demonstrated that the patients responded well to the social support and interaction with staff in a calm, anxiety-free environment.[5]

The social-setting philosophy of detoxification and the programs that spread from Toronto verified that a nonmedical staff trained to recognize possible medical complications and backed up by a general hospital could provide a safe, effective and cost-efficient alternative.[6] Daily costs per patient were dramatically reduced to generally less than 25% of the costs of a hospital day.[7] Referral to on-going treatment and service programs for further recovery assistance became a major focus in the social-setting philosophy and created the potential to reduce recidivism.

The State of North Carolina began a plan through which inebriates would be provided detoxification services in the least restrictive setting, close to their own community. In 1983 the State hospitals (John Umstead, Cherry, Dorothea Dix, Broughton, and the Detoxification Unit at the Black Mountain Alcoholic Rehabilitation Center) began to close their doors to inebriates who exhibited no psychiatric disorders. State funds were transferred to local communities for the development and provision of social-setting residential detoxification facilities.

To meet the challenge of providing safe, cost-effective care, the social-setting detoxification facility must have consistent, responsive medical backup to attend to the 5% of patients needing inpatient observation. The Mountain Area Health Education Center Family Practice Residency Program and the Blue Ridge Center for Mental Health, Mental Retardation and Substance Abuse Services have cooperated to create a unique social-setting/medical model that has utilized an innovative approach resulting in dramatic inpatient cost reductions.

An Alternative Model

Inebriated patients arrive at the Blue Ridge Mental Health Neil Dobbins Social Detoxification Center on referral by self, family, physician, A.A., medical facility, or law enforcement agency. Their initial evaluation includes an extensive medical and psychosocial history to assess the severity of complications due to alcoholism and underlying medical and psychiatric illness. Patients with significant cardiovascular disease, polyaddiction, history of life-threatening symptoms of withdrawal, or other major medical concerns are referred for evaluation by a Family Practice resident physician. There are no physicians or nurses at the social-setting detoxification facility; health care technicians monitor vital signs. The personnel at the Dobbins Center may not adminster any medication. They do remind the patients to take their chronic medication at the prescribed times. No patient is admitted who requires tapering sedatives, parenteral medication, or newly instituted psychotropic drugs.

Patients are admitted to the residential unit for three to

From Mountain Area Family Health Center, 491 Biltmore Avenue, Asheville 28801.

five days. From the day of admission they are involved in a supportive, but directive, rehabilitation process that includes individual and group therapy, A.A. meetings, and arrangements for involvement of the patient and the patient's family in aftercare. Patients are responsible for housekeeping tasks during their stay.

Those patients referred for medical evaluation are seen by resident physicians from the MAHEC Family Practice Residency Program in the emergency room at Memorial Mission Hospital. Consultation is available from the resident physicians 24 hours per day; this experience is an integral part of the Residency Program's curriculum in addictions.

Patients requiring admission to the hospital are placed on the Family Medicine inservice and are supervised by one of four rotating attending faculty. All patients admitted from the social detoxification center are placed on a protocol that has features that surprise many who were schooled in the traditional medical detoxification model. None of the patients receive intravenous medications and none are given benzodiazepines.

The protocol is an adaptation of one utilized by Dr. John Mooney at Willingway Hospital in Statesboro, GA (see Appendix A). By avoiding intravenous treatment, costs and nursing time are reduced significantly. Although some were clinically volume depleted, all our patients were able to adequately rehydrate themselves orally. There is evidence to support the view that many cases of "DTs" are actually iatrogenically-induced symptoms of cerebral edema from overzealous intravenous hydration. Phenobarbital has multiple advantages over benzodiazepines[8] including antiseizure effects when administered orally.

The patients admitted to the hospital were begun on the protocol and observed for progression or resolution of symptoms. If symptoms of impending DTs quickly abated, the protocol was suspended, and following appropriate observation the patient was returned to the social detoxification unit — on no mood-altering drugs. If signs and symptoms of DTs persisted or progressed, the protocol was continued. When the inpatient treatment for DTs was complete, the patient was referred to the social detoxification unit, without sedatives or other mood-altering drugs.

Results

Between September 1984 and February 1985 there were 400 admissions to the Dobbins Center Residential Social Detoxification Facility (table 1): 70% of the admissions were "one-timers"; 30% of the admissions were "recidivists."

The 400 admissions required 51 evaluations by a physician. Some of these involved simple treatment of lacerations or refill of prescription for chronic antihypertensive medication. Twenty of the patients evaluated were admitted for inpatient observation and treatment at Memorial Mission Hospital. The average length of stay was 1½ days, for a combined total of 31 hospital days!

None of the patients admitted to the hospital required rehospitalization during the study period. There were no deaths, no Intensive Care beds were utilized, and there were no complications of therapy.

Of the 400 admissions to the Dobbins Center, 320 individuals were involved in the study population; 127 (40%) of these were entered in alcoholic rehabilitation programs in addition to Alcoholics Anonymous.

Table 1

Statistics of Admissions to the Neil Dobbins Social-Setting Detoxification Center September 1984 through February 1985

	Male	Female	Total
Admitted	345	55	400
Individuals involved	280	40	320
Physician referrals	38	13	51
Patients hospitalized	17	3	20
Hospital days	23	8	31
Discharge Referrals			
A. 28-day program	34	8	
B. Outpatient counselling	24	3	
C. Halfway house	10	2	
D. First Step Farm	12	—	
E. Western Carolina Rescue Mission	11	—	
F. Long term	1	—	
G. VA program	22	—	127

Discussion

Treatment of the alcohol withdrawal syndrome utilizing the traditional medical model is expensive, frustrating, and fraught with complications of therapy and a high rate of recidivism. Social setting detoxification has proven itself effective and cost efficient, but must have dependable medical backup. In our series 13% of the admissions to the social-setting detoxification center required physician evaluation and 5% required hospitalization. These data are consistent with the experience in Toronto as described in the introduction.[1]

The remarkably brief average length of hospitalization in this study deserves further discussion. The population admitted to the hospital represented the 5% at highest risk; among this group were patients with seizure disorders, marked coronary artery disease, prior documented history of DTs, psychiatric disorders, intercurrent pyelonephritis, and severe hypertension. Histories were not always reliable, and noncompliance with prior medical advice and therapy was the norm.

The protocol as described in Appendix A minimized iatrogenic complications and effectively managed symptoms. No seizures occurred with this protocol and all patients were ambulatory within 18 hours of admission.

The success of early transfer to the social-setting detoxification center was made possible by the shared philosophy to minimize drug administration during the withdrawal phase. Hospitalized patients who would not have been ready for discharge home could be transferred to the social-setting unit where skilled observation and enforced abstinence occurred.

The medical aspects of alcohol withdrawal are only a small part (albeit traditionally expensive) of the rehabilitation of the alcoholic. Long-term success is dependent upon coordination of all aspects of the rehabilitation process. Drugs that inhibit or delay sobriety must be limited to treatment of life-threatening symptoms. Drugs used in treating the withdrawal syndrome are dulling and have a negative effect on selfcare and sociability of the alcoholic and may inhibit a clearheaded self-appraisal and acceptance of rehabilitation. Drugs may become associated with the relief of painful symptoms in the alcoholic; this may reinforce dependency on drugs and especially on the use of alcohol to cope with stressful situations.[9]

The social setting detoxification program utilizes the discomfort associated with withdrawal in a positive fashion to reinforce the disease concept of alcoholism and to underscore the alcoholic's responsibility for the consequences of his/her actions. This attitude that the alcoholic is responsible for his/her recovery must pervade both the social setting and the medical setting. The patient should participate in his/her recovery throughout the process, and should not be excused to passively receive treatment in the hospital.

The fact that no patients required rehospitalization during the study period reflects admirably on the Dobbins Center intervention. A high percentage (40%) of patients were enrolled in specific aftercare programs to supplement involvement in A.A.; 289 persons did not require readmission to the Dobbins Center. Early readmission to the social-setting unit cannot be construed as a failure if it obviates hospitalization.

The cooperation between the Blue Ridge Mental Health social-setting detoxification unit and the MAHEC Family Practice Residency Program inpatient service has resulted in an effective, cost-efficient alternative to treat the alcohol withdrawal syndrome.

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Appendix A
Routine Medical Detoxification Protocol*

1. Admit to medical floor. Dx. — Alcoholism, alcohol withdrawal syndrome. depression.
2. Condition — guarded.
3. Constant observation by attendant for ____ hours.
4. Darken room, night light on, bedrails up, urinal at bedside, BRP with assistance only.
5. Vital signs — orientation, pulse, respiration, temp., BP, q____H ×____Hrs.
6. Diet — as tolerated. Fluids and snacks at bedside.
7. Admission Lab — CBC with platelet count, electrolytes, glucose,
   UA — STAT
   CBS-22; CXR and EKG when stable.
   Blood alcohol level. Urine drug screen.
8. Phenergan 50 mg IM on admission. Thiamine 100 mg IM on admission.
9. $MgSO_4$ 1 g IM q 8 h × 6 doses.
10. Phenobarbital 60 mg TID × 2 days, then
    30 mg TID × 2 days, then
    15 mg BID × 1 day
11. Sodium Luminal Gr. II to IV IM PRN agitation × 1.
12. Vistaril 50-100 mg IM PRN anxiety × 1.
13. Tylenol Gr × q 4 h PRN headache
14. Robaxin 750 mg qid PRN muscle cramps. P.O.
15. Nembutal 50 mg P.O. or IM qHS PRN sleep. May repeat × 1 after 30 min.
16. Call physician for:
    (1) marked agitation/change in mental status;
    (2) temp. greater than 100.4;
    (3) pulse greater than 100 on two occasions or for upward trend in pulse or BP;
    (4) BP greater than 170/95.
17. No visitors

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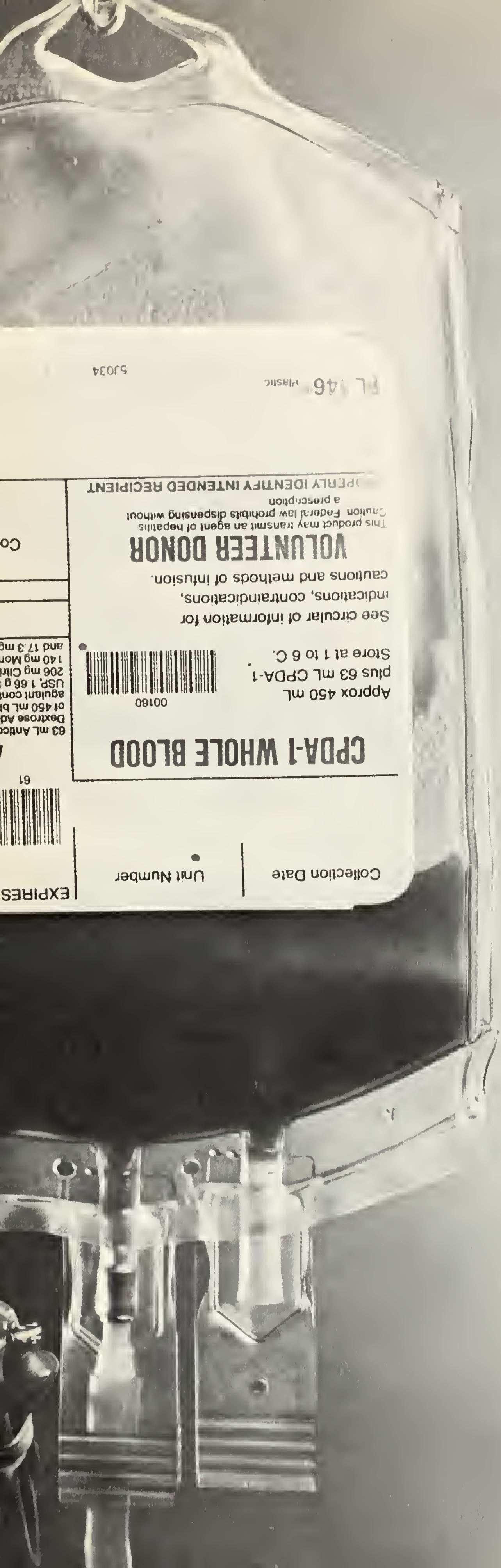
*Adapted from Willingway Hospital, Statesboro, GA



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IN STATE

September 13
Medical Staff Legal Status: Independent or Dependent?
Place: Greenville
Credit: 8 hours Category I AMA
Info: Office of CME, ECU School of Medicine, Box 7224, Greenville 27835-7224. 919/758-5200, ext. 208

September 17
Crisis — Then & Now
Place: Asheville
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 800/662-7917

September 18
Echocardiography and Doppler Carotid Examinations
Place: Sanford
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage Street, Sanford 27330. 919/774-6518

September 18-22
New Horizons in Pediatric Urology
Place: Pinehurst
Credit: 25 hours Category I AMA
Info: Linda Mace, Box 3707, DUMC, Durham 27710

September 19-21
Surgery of Facial Skeleton
Place: Charlotte
Info: Ellison F. Edwards, M.D., 3535 Randolph Road, Charlotte 28211

September 23-November 15
Postgraduate Courses in Medical Sonics
Place: Winston-Salem
Credit: 35 hours per week Category 1 AMA
Info: Dianne L. Willard, Bowman Gray, Winston-Salem 27103. 919/748-4505

September 24
Crisis — Then & Now
Place: Greenville
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 800/662-7917

September 27-28
Advanced Cardiac Life Support Provider Course
Place: Asheville
Credit: 16 hours Category I AMA, ACEP, 16 prescribed hours AAFP
Fee: $200
Info: Daniel L. Dolan, M.D., MAHEC, 501 Biltmore Avenue, Asheville 28801-4686. 704/258-0881

October 2
Crisis — Then & Now
Place: Kinston
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 800/662-7917

October 16
Oxygen Use — CO_2 Narcosis and Ventilator Use
Place: Sanford
Credit: 2 hours Category 1 AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

October 19-20
Jungian Techniques of Analytic Hypnotherapy
Place: Chapel Hill
Credit: 12 hours Category 1 AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

October 29
Crisis — Then & Now
Place: Kinston
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 800/662-7917

November 1-2
Alcohol and Drug Abuse
Place: Chapel Hill
Credit: 10 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

November 1-2
Review of the Management of SIDS and Near-Miss SIDS
Place: Chapel Hill
Credit: 7 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

November 20
Endocrinology for the Lifetime of the Female
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

OUT OF STATE

September 5-7
Doppler Echocardiography Seminar
Place: Isle of Palms, SC
Credit: 16 hours Category I AMA
Info: Dianne L. Willard, Bowman Gray, Winston-Salem 27103. 919/748-4505

September 12-14
Advanced Applied Ultrasound in Obstetrics Seminar
Place: Myrtle Beach, SC
Credit: 12 hours Category I AMA
Info: James F. Martin, M.D., Center for Medical Ultrasound, Bowman Gray, Winston-Salem 27103. 919/758-4505

October 4
Selected Topics in Pediatrics
Place: Norfolk, VA
Info: Jean E. Shelton, M.D., 800 West Olney Road, Norfolk, VA 23507. 804/628-3798

October 5
Advances in Human Genetics and Reproduction
Place: Arlington, VA
Info: Brenda English, 3300 Gallows Road, Falls Church, VA 22046. 703/698-3481

October 17-24
Review of Clinical Chemistry for Practicing Pathologists and Clinical Chemists
Place: San Diego, CA
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October 29-November 2
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Letters to the Editor

To the Readership from the Managing Editor

You may have noticed that the July NCMJ reached your eager clutches just barely under the wire — July 30 if you were lucky, July 31 otherwise. We do apologize. The July issue was designed to include a 24 page central article, removable via a process that involves triple stapling with three separate journeys through the bindery. Because of a very great number of changes needed in that article at the very last minute, we had to pull it from the July issue and will publish it in October. To accommodate the loss of 24 pages, our valiant printers had to repaste the entire issue, moving inserted ads to balance front and back, and, in particular, moving the internal color to appear in the same 16-page signature to save money. The issue, printed and bound, left our printer in Fulton, MO, on the afternoon of July 22. Where it spent the next seven or eight days is a mystery even the Postal Service cannot solve. We apologize for our part in the delay. The Postal Service has no comment.

Patricia Hodgson
Box 3910
Duke Hospital
Durham 27710

An Open Letter to the President of R. J. Reynolds Tobacco Company

As a retired physician who practiced for many years in North Carolina I am deeply committed, as I am sure you are, to promoting the health of the people of our State. The notable contributions of the Duke Foundation to that end have been a credit to your industry. However, a recent issue of the *Journal of the American Medical Association* contains a number of papers which reflect the studied opinion of my profession on the role of tobacco in serious diseases, an opinion based on thirty-five years of careful observation and research.

The growing, processing and sale of tobacco and its products plays such an important part in the economy of our State that no one should damn it without offering reasonable alternatives. As a starter, may I offer the following suggestions?

1. That the R. J. Reynolds Tobacco Company take the lead and establish a foundation to discover and develop an alternative crop to tobacco which our farmers could profitably grow;
2. That your Company search out and develop an alternative industry, utilizing the talents of your management personnel and the energy of your workers with long-term benefits to all concerned;
3. That a time schedule be set up during which a gradual conversion could be completed, one that could be long enough to cover the life span of persons already dependent on tobacco with immediate cessation of efforts to encourage use by the young;
4. And that this or a similar program be actively publicized in order to receive the well deserved good will and support of the public.

Please favor me with your reaction. I am taking the liberty of sending you a copy of the recent *Journal of the American Medical Association*.

Alex S. Moffett, M.D.
70 West Lucerne Circle
Orlando, FL 32801

Editor's Comment

The insistence of the leaders in the tobacco companies that there is no link between cigarette smoking and cancer and emphysema does a great disservice to the image of American industrialists. They show us every day the force of self-interest and make us distrust all statements made by industrialists about safe working conditions and the safety of their products.

Eisenhower's statement that we were not spying on the Russians with our U2 airplane destroyed some of our simple faith in statements by our government. The tobacco companies' refusal to face honestly the links between diseases and cigarette smoking destroys our faith in industrial leadership. Until the tobacco companies face this issue squarely, they will do nothing to help our small farmers create a new money crop.

WWII Duke: COs, POWs, V-12, ASTP et al

The article about the conscientious objectors (NCMJ 1985;46:419-23) at Duke by Louis Swanson and James Gifford brings back memories. We had an unusual conglomeration at Duke during that time. As noted, there were the conscientious objectors. Most of the medical students were either in the V-12 Navy program or the ASTP Army program and were in respective military uniforms. Dr. Robert (Daddy) Ross continued his OB practice, along with commanding the Navy unit at Duke.

Another interesting group were the German soldiers who worked at Duke Hospital during the last part of the war. These prisoners of war were transported back and forth from Camp Butner. Although I don't remember the exact words, I do remember interesting conversations with the German POWs who could speak English, the conscientious objectors, and we medical students who were in the Navy and the Army. The thing I remember most is the inquisitiveness that each had about the other. A more exact, detailed documentation of those encounters would be quite interesting.

Thomas B. Dameron, Jr., M.D.
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Raleigh 27605

Family Medicine at Duke: Another View

As a Family Physician, I have read with great interest the special article regarding Family Medicine written by Dr. Robert Sullivan in the June 1985 issue of the *North Caroli-*

na Medical Journal (NCMJ 1985;46:329-31). It is obvious that the article was written to present Duke Medical Center's viewpoint. Just enough historical data is presented to make the casual reader believe this to be an unbiased and factual report.

Far from it. The author is from the Department of Medicine which presented the greatest opposition to Family Medicine and to a favorable solution to the problems. Many of the statements in the article deserve comments.

The author states many are "skeptical that one person can know enough to do the job well." Not all graduates of any specialty residency perform their job well, but the track record of graduates of Family Practice Residency Programs across the country has been a record of quality care. Family physicians are required to obtain 150 hours of approved postgraduate education every three years to maintain membership in the American Academy of Family Physicians. Further, the certification by the American Board of Family Practice requires re-certification every six years. These educational requirements contribute to the quality care of Family Physicians.

Another statement in the article, "Logic dictated the new program be placed in the local community hospital." This move may have been good for the program, but showed a lack of commitment by Duke from the first. Later, the various departments accused the Family Medicine Program of being disloyal to Duke because they hospitalized their patients at Durham County Hospital and used local consultants rather than the facilities at Duke Hospital. However, the clinical departments have consistently opposed admitting privileges to Family Physicians. How many physicians would be happy to admit their patients to a hospital where they can have no part in the care of their patients?

Another statement, "Family Medicine (holistic, integrative, and humanistic) challenged deep-rooted traditions in academic medicine and clinical practice." There are deep philosophical differences between the disciplines, but if academic medicine does not believe in bonding between patient and doctor, and the continuity of care of patients, then in my opinion, academic medicine is far off course. This statement, in my opinion, represents a group of physicians who have not experienced on-going contact with a patient in years — if ever.

The article deserves many more comments, but because this is a letter to the editor instead of a special article, I will instead offer a few comments of my own.

The Lewin & Associates External Review offered four options:

1. Status quo.
2. Strengthen the Department of Community and Family Medicine, directing other departments to accept its role and integrate it more fully into the Medical Center.
3. Eliminate Family Medicine as a primary care discipline, and replace it with a new integrated program in primary care under the Departments of Medicine, Pediatrics, and OB-Gyn.
4. Eliminate all primary care programs, and accept a role as a purely tertiary institution.

Option 2 was recommended by the report. As we know, Option 3 was selected by the Duke Medical Center. I fail to understand how departments that have opted for subspecialty training and have no experience or understanding of primary care can run a program in primary care. I might further point out that Duke has never been known for its cooperative interaction between departments. This would be another point against the success of a primary care program under these specialty departments.

Was Family Medicine "destructive to the fabric of the organization?" I hardly think so. The Family Practice Residency graduates have contributed greatly on a statewide basis. The statement relating to the destruction of forces to the fabric is presented in part because of economic problems resulting from decisions by self-centered departments. The cause of these problems is still present at Duke.

No, Dr. Sullivan — this will not pass as did the decisions on the School of Nursing and Education. Today, we are dealing with the health needs of North Carolina — not the selfish interests of various departments in Duke Medical Center. The people of North Carolina will not let this pass. Duke should *not* let this pass. Did Duke truly make the attempt to support the Family Medicine Program or was it just in name only?

We need sub-specialists in all fields. No one, particularly Family Physicians, deny this fact. But we also need the generalists — the Family Physician, the general Internist, and the general Pediatrician. The people of North Carolina need these physicians for quality health care. We must put aside personal differences and work together for the good of North Carolina. The citizens of North Carolina deserve quality health care in every hamlet and county of the state. I hope Duke will reconsider.

George T. Wolff, M.D.
1016 A Professional Village
Greensboro 27401

And Another

I would like to take a second look at Dr. Robert Sullivan's article (NCMJ 1985;46:329-31) justifying Duke's decision to terminate its Family Medicine Program. Dr. Sullivan pointed out most of the pertinent facts of the case quite accurately. I would like to briefly reiterate those facts.

Following a nationwide trend, Duke created a Department of Family Medicine in 1972, but "it was not done with unanimous faculty acclaim." Duke University Hospital was already crowded with referral patients and did not want the Family Practice Program. Durham County Hospital, the nearby community hospital, did want the program.

Not only was there lack of faculty acclaim for Family Medicine and lack of Duke University Hospital support for a Family Medicine Program, Duke went so far as to make the medical center completely off limits to Family Physicians. Family Physicians, whether residents or faculty, did not have admitting privileges at the Duke Medical Center. Since at Family Medicine's inception Duke had a monopoly on specialty care in Durham County, at first residents and faculty had no choice but to send their patients to Duke. However, in the following years, private subspecialty care flourished in Durham County. With the availability of excellent private consultants, Family Medicine patients then went to Durham County Hospital where the residents and faculty could admit and care for their own patients with appropriate consultation. The Family Practice program could practice comprehensive and continuous care only at Durham County Hospital.

Family Medicine at Duke University was a success. Both Family Medicine trainees and their graduates helped to fill health manpower shortages in North Carolina. Also Family Medicine was a success in attracting state dollars through the AHEC system. Family Medicine was a success despite lack of support of the University Hospital and continued "internal problems."

As economics changed, Duke University Hospital wanted and needed the patient population served by the Family Practice program. In 1972 Duke University Hospital was "already overcrowded with referral patients." In 1985, they were faced with attracting patients in an increasingly competitive health care market. An independent study emphasized that the Duke Family Medicine program was successfully competing in the marketplace. In fact, this successful competitor was just what Duke University Hospital needed to reach out to the community and rural physicians. Duke University Hospital needed Family Practice to keep up with the changing economic market.

But, "internal problems persisted." "Duke Medical Center Internal Medicine, Pediatrics, and Obstetrics/Gynecology house officers and attending physicians . . . had trouble understanding the orientation of Family Medicine house officers who had been carefully selected for their intellect, orientation to patients, and their families, and commitment to community needs."

"The Medical Center faced a clear choice." It could either maintain the program's isolation or it could fully accept Family Medicine at Duke. If it chose to maintain its isolation, the Family Medicine Program would continue to successfully compete for patients and refer them to Durham County Hospital where they could fully participate in their inpatient care. It could also fully accept Family Medicine at Duke allowing the Department to have admitting privileges at Duke University Hospital. Instead Duke chose to close the Family Practice Clinical Program and have their patients usurped by "newly expanded primary care divisions within the departments of Medicine, Pediatrics and Obstetrics."

These are the facts delineated by Dr. Sullivan. I have not added anything to his argument. I have deleted certain arguments which I do not consider valid. For example I do not consider the resignation of a single faculty member sufficient reason to close any department. In reviewing these facts, I reach a different conclusion than Dr. Sullivan. Family Medicine has never been accepted by Duke. They eliminated a source of patient care competition by eliminating a successful Family Practice Program. They did this instead of fully accepting Family Practice at Duke. In my mind, Dr. Sullivan's arguments damn rather than justify Duke's actions.

William A. Hensel, M.D.
Moses Cone Family Practice Center
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Editor's Note

Dr. Sullivan served as Vice Chairman of Family Medicine at Duke from 1974 to 1980.

Each Person Can Make a Difference

I think our society has been discussing the wrong subject. Instead of debating the pros and cons of voluntary abortion, we should focus attention on coercive ways to limit our population. So I wrote the following Letter, titled Abortions and Overpopulation, which was published in the *Greenville Daily Reflector,* May 24, 1985:

> To discuss abortions without mentioning overpopulation is like discussing fish without observing that fish live in water.
>
> Abortions are not performed in operating rooms in the sky. They take place in societies which have limited capacities to raise, care for, and provide a satisfactory life for new offspring.
>
> The Chinese do not promote abortions because they like to destroy Chinese fetuses. Instead, the Chinese are compassionate and intelligent. They realize their capacity to provide a satisfactory life for children is limited. Regardless of how intensively cultivated, their land can grow only so much food. Abortions are better than having infants and small children die of starvation and related diseases.
>
> The United States already has evidence of severe overpopulation. We have a twin deficit of budget and trade. We live partly on borrowed resources, oil produced in other countries. We have a drug problem. We have a growing prison population, many of whom could not find a place in society. Some old people live in poverty and financial insecurity.
>
> Fish do live in water. Abortions do take place in societies. To properly evaluate abortions, we should examine the entire picture, not just an isolated part of it.

Before I even saw the Letter published, I received a phone call. The lady claimed that, according to the geography department at East Carolina University, the USA was not overpopulated. I suggested they write a Letter opposing mine.

The big advantage of a democratic country is the ability to publicly express one's views. The opposition should have equal opportunity to be heard.

A second phone call, about an hour later, was from a woman who accused me of being a murderer and hung up.

The third call came a few minutes later. An older lady thanked me for writing the letter.

You may agree or disagree with my views on abortion and overpopulation. In either case, I hope you have an equal chance to express your opinion.

An organized group, of course, has more power than isolated individuals. But the point remains — so long as we have access to a free press, one person willing to write and answer the phone can make a difference.

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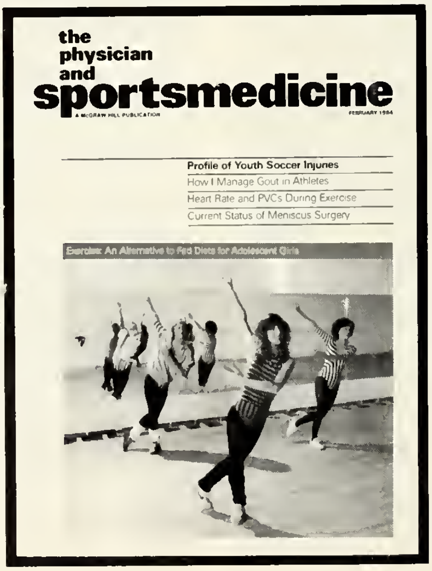

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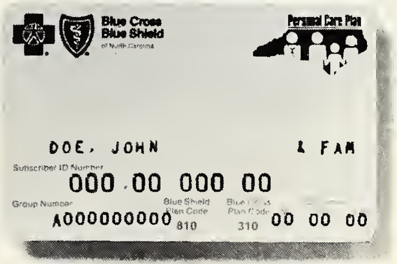

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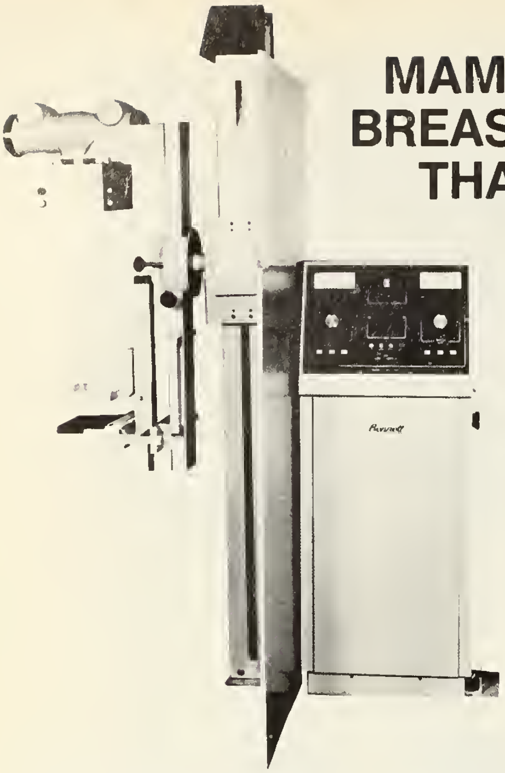

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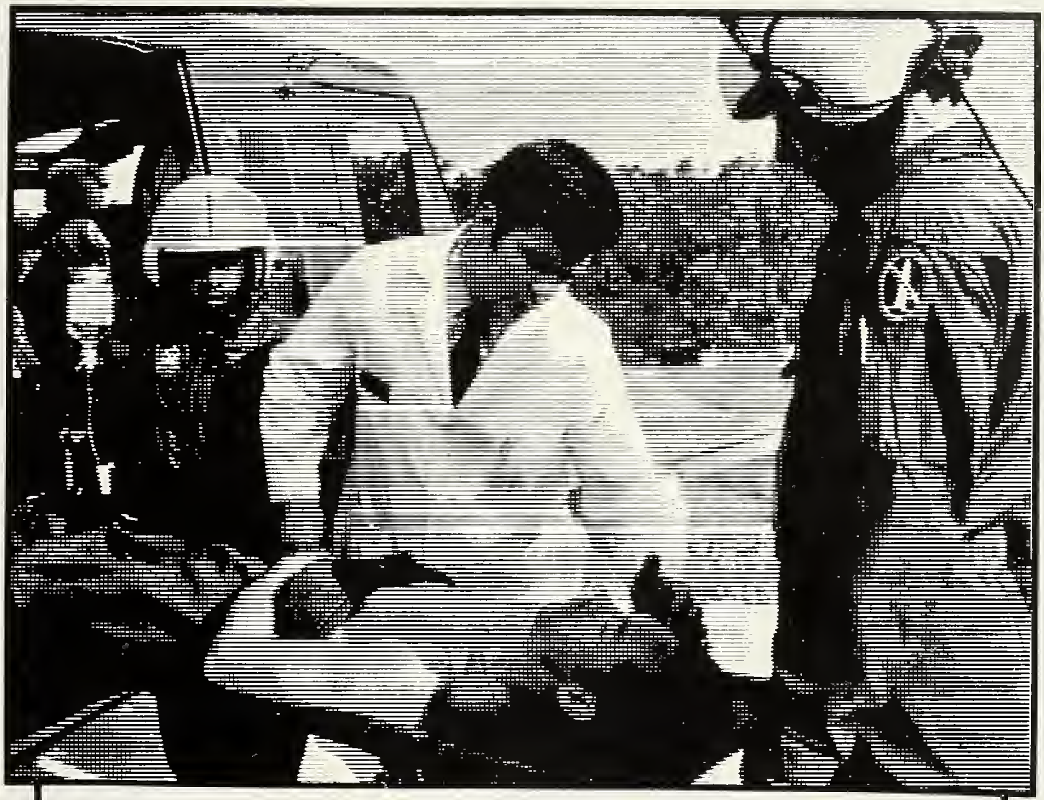

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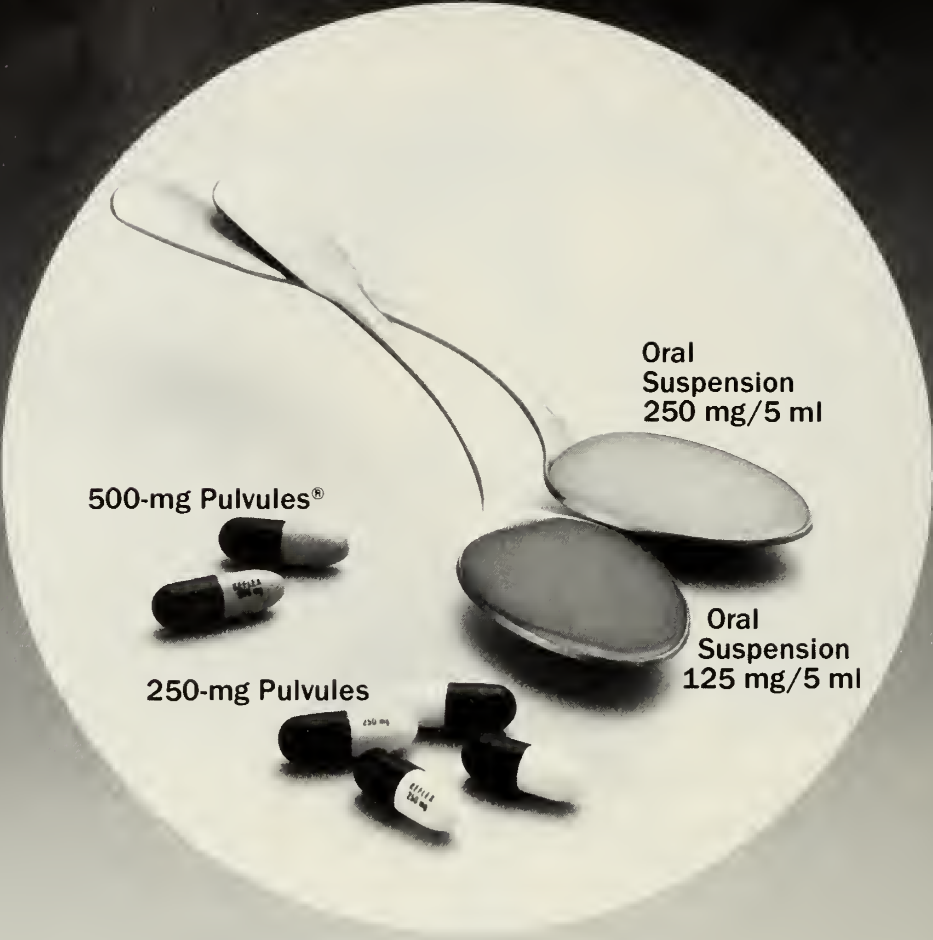

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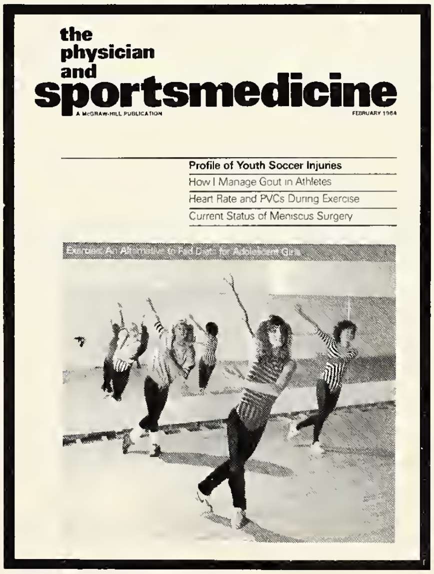
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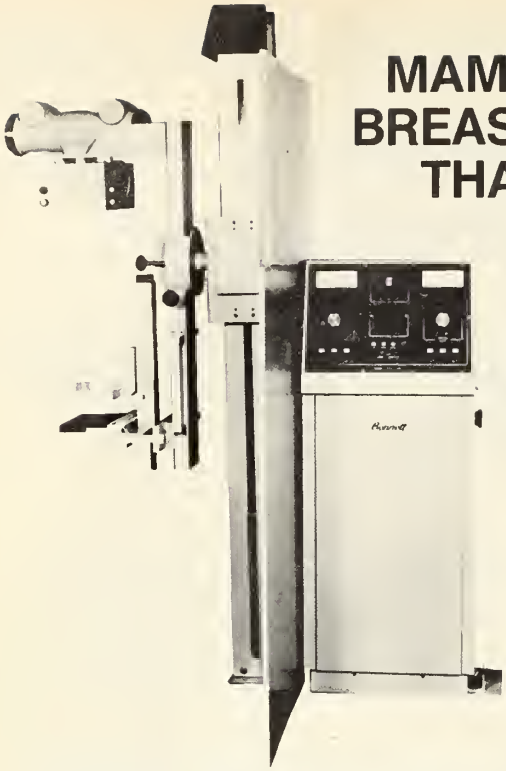

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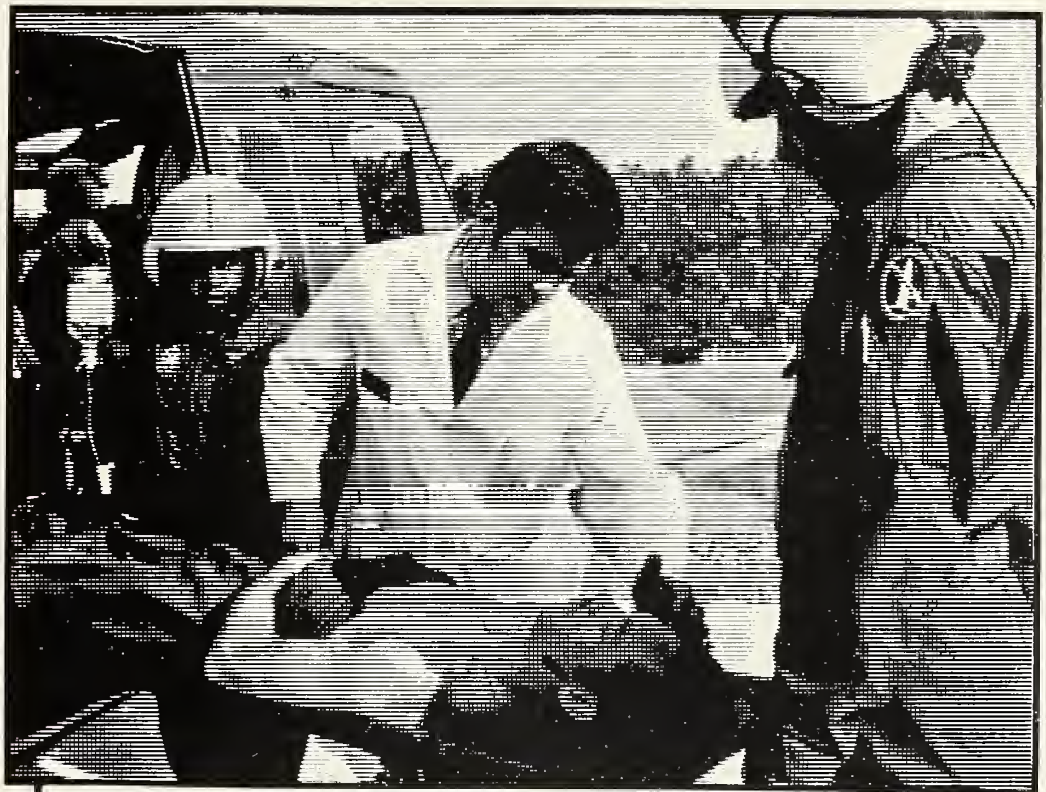

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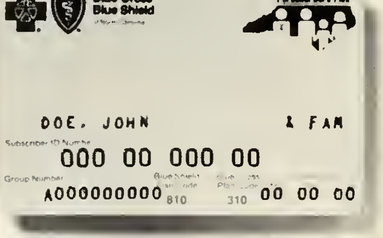

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Keith V. Nance, Irwin S. Johnsrude, M.D., Michael B. Kodroff, M.D. and Jan F. Silverman, M.D.

- *Fine needle aspiration is a safe, quick and reliable biopsy method.*

APPROXIMATELY ninety fine needle aspiration biopsies of deep abdomen, retroperitoneum, soft tissue, and bone have been performed at East Carolina University School of Medicine/Pitt County Memorial Hospital over the past five years, with 62 biopsies occurring during 1984. The purpose of this paper is to report our experience (1984) and to encourage the use of percutaneous fine needle aspiration biopsy of deep abdomen, retroperitoneum, soft tissue, and bone as a diagnostic procedure.

Materials and Methods

The procedure is similar to methods previously described.[1-4] Before the study, informed consent is obtained following discussion of the possible complications of the procedure. Mild sedation is usually given. Old and recent films, particularly ultrasound and computed tomography (CT) studies are reviewed.

Ultrasound is generally the preferred radiologic guidance method. The procedure has lower cost, greater speed and flexibility, and requires no ionizing radiation. Special transducers used for guiding the needle add to the simplicity and accuracy of this approach. Computed tomography has the advantages of reproducible excellent resolution and superiority over ultrasound in localizing small, deep lesions and visualizing needle placement in some solid masses. CT is now delegated to a secondary guidance method due to its relatively high cost, significant radiation exposure, and slower, more cumbersome technique.[4] The advantages and disadvantages of ultrasound and CT are detailed in table 1. Fluoroscopic guidance was used in this study for aspiration of bony lesions. Supplemental use of CT or ultrasound occasionally aided in determining the depth to which the needle was inserted and the angle of entry for bony lesions.

An entry site is selected that will attain the shortest distance between skin and the lesion to be aspirated while avoiding other major structures. The depth needed for the needle's penetration is determined and this measurement is indicated on the biopsy needle. The skin surface is cleansed with Betadine, local anesthesia is injected into the skin, followed by a small skin stab wound. A 22-gauge (0.6 mm) biopsy needle is then guided into the lesion. As the needle tip enters the lesion the radiologist often can detect a change in the consistency of the tissue. With real time ultrasound the needle tip can be visualized as it enters the lesion. When the needle point has been placed in the desired position, the stylet is removed, a 20 cc syringe is attached, and the needle is moved to and fro with suction applied. The vacuum is released before the removal of the needle, and both the needle and syringe are withdrawn. The syringe is then detached from the needle, filled with air, and reattached and the needle contents are expressed onto the center of the sterile frosted end-glass slide. An assistant usually helps prepare the slides.

Table 1
Advantages and Disadvantages of Radiologic Techniques

Fine Needle Biopsy with Ultrasound
- No radiation
- See mass as needle enters it (93% accuracy)
- Needle trajectory on the screen
- Angle calculation unnecessary
- More expeditious (and less costly) than CT
- Can be done outside Radiology Department
- Operator dependent
- Gas and obesity are limitations

Fine Needle Biopsy with CT
- Documents needle position despite:
  - Gas
  - Obesity
  - Dressings
  - Small size lesion
  - Proximity to vital structure (pleural, vessels)
- Aspiration and drainage of fluid collections
- Time consuming, radiation exposure, expensive

The smear technique consists of compressing the material on the slide with another slide and spreading this material over a small area similar to the preparation used in bone marrow aspirate. The majority of the smears are immediately wet fixed in 95% alcohol while a few others are air dried. One or more of the air dried smears are immediately delivered to the pathologist who performs a rapid modified Wright stain (Diff-Quik). The staining pro-

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Table 2
Indications

Establish diagnosis of a clinically or radiologically detected mass:
- Malignant — Primary — stage
  - Inoperable patient
  - Recurrent or metastatic
  - Determine operability and therapy plan:
    - Surgery
    - Radiotherapy
    - Chemotherapy
- Benign — Evacuate: Cyst
  - Abscess (culture)
  - Granulomas, i.e., TB, fungus
  - Granulation tissue

cess takes approximately 20 seconds and slides are examined wet. The pathologist will then assess the adequacy of the sample and whether additional aspirations need to be performed. The pathologist usually gives his preliminary diagnosis in person in the radiology department procedure room where he can review the x-rays and directly confer with the radiologist. The immediate "quick read" procedure can easily be performed within five minutes. At this time, any additional material can be allocated for further studies including microbiologic examination, cell block and electron microscopy. The remaining 95% alcohol fixed slides are examined within one or two hours and the final diagnosis is rendered. The pathologist contacts both the radiologist and the patient's physician. Following the biopsy procedure, the patient is observed for any signs of complications including bleeding, and vital signs are recorded. Indications for fine needle aspiration biopsy at ECU/PCMH are outlined in table 2.

Results

Fifty-four patients underwent sixty-two biopsies at Pitt County Memorial Hospital in 1984. The age range was 23 to 88 years old with a mean age of 62. There were 26 men and 28 women. Thirty-one specific malignant diagnoses were rendered. There were thirty-one negative cases. Five of the negative cases were later shown to be malignant by histologic examination for a false negative rate of 14%. There were no false positive diagnoses. The sensitivity of the procedure (true positive) was 86% and specificity (true negative) was 100%. In fifteen negative FNA biopsies (48%), a specific non-malignant diagnosis was rendered. There were no complications reported following any of the fine needle aspiration biopsies presented in this study.

Discussion

The main value of fine needle aspiration biopsy of deep abdomen, retroperitoneum, soft tissue, and bone is in the diagnosis of malignancy. An accuracy rate of 80 to 90% is reported in most series which is exemplified by our 1984 experience, where a diagnosis of malignancy was made with a sensitivity of 86% and a specificity of 100% for the procedure.[1-13] In addition, the procedure can serve as an accurate means of diagnosing malignant lymphoma as evidenced by our experience with five cases in this study. Fine needle aspiration biopsy is particularly useful in cases where there is a question of recurrence of a previously diagnosed malignancy. Our results also support the role of FNA in diagnosing non-malignant conditions. Forty-eight percent of our negative cases had a specific non-malignant diagnosis.

Continued refinement of radiologic guidance techniques, particularly the development of special aspiration transducers for ultrasound which are capable of simultaneously guiding needle placement and imaging regional anatomy, should lead to continued improvement in accuracy of this procedure.

Our experience in this study re-emphasizes that fine needle aspiration biopsy of deep abdomen, retroperitoneum, soft tissue, and bone is a safe and quick means of diagnosing both benign and malignant lesions and is both less expensive and less invasive than other currently available modalities. The procedure causes little discomfort to the patient and can be performed in both out-patient and hospital settings. FNA biopsy of deep, non-palpable lesions utilizing sophisticated radiologic technique offers an accurate means of diagnosis which minimizes delay in treatment. The procedure works best when the expertise of the cytopathologist, radiologist, and primary physician are combined in a team effort.

References available from the authors.

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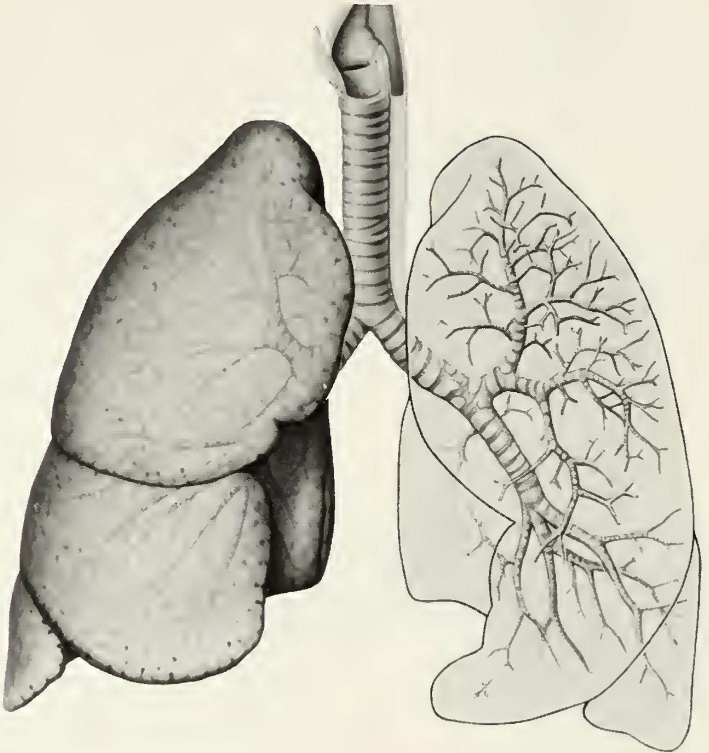

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Indications and Usage Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

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Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should be ruled out

Precautions: *General Precautions* – If an allergic reaction to Ceclor® (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e g , pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy – Pregnancy Category B – Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor® (cefaclor, Lilly) There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers – Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses Average levels were 0 18, 0 20, 0 21, and 0 16 mcg/ml at two, three, four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known Caution should be exercised when Ceclor is administered to a nursing woman

Usage in Children – Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1 5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain – Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic – Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic – Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal – Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

Note Ceclor® (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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SCIENTIFIC ARTICLE

Looking at Renal Failure Upside Down

Jeremy Sugarman, Gail Belinsky, M.D. and Francis A. Neelon, M.D.

PROGRESSIVE renal insufficiency has a way of humbling the average physician. Though it is not usually difficult to diagnose "renal insufficiency" or "nephrotic syndrome," it can be extremely difficult (and sometimes impossible) to ascertain their underlying causes. Hence, progressive renal insufficiency provides a diagnostic challenge, often answered by frustration. Hippocratic physicians would not have joined us in this frustration. "The Hippocratic physician was primarily interested, not in diagnosis, but in prognosis and treatment. His first interest was not in a disease manifested in the patient, but in the patient himself. He was concerned with the body as a whole rather than with the lesion of the parts. Here, he partly transformed a shortcoming into a virtue. His knowledge was far too limited to practice diagnostics and specific treatments successfully."[1]

When dealing with a process as complicated as progressive renal failure it would be helpful to have an easier means of monitoring the course of the illness and the response to various treatments than the calculation of creatinine clearance with its cumbersome necessity of repeatedly collected 24-hour urine specimens which demand diligence, compliance and sometimes extraordinary gymnastics. The following case history illustrates some of the problems encountered in caring for a patient with the nephrotic syndrome and progressive renal failure while illustrating a simple means we used to follow her course:

A twenty-six-year-old black woman felt well until early April 1985 when she noted the gradual onset of swelling in her legs and abdomen over the course of about one week. During this time period, she had occasional nausea, vomiting, and loose stools. On April 12, 1985, she came to the emergency room where her serum creatinine was found to be 1.6 mg/dl (normal value 0.7-1.4) and BUN 18 mg/dl (7-21). A routine urinalysis showed pH, 7; specific gravity, 1.020; 4+ protein; 1-5 WBC; 3+ bacteria; 0-1 WBC casts; 0-2 hyaline and granular casts per high power field. A urine specimen sent for culture was lost. Because of the possibility of urinary tract infection, she was given trimethoprim-sulfamethoxizole twice daily.

On April 20, 1985, she returned complaining of diffuse abdominal pain. She admitted using acetaminophen for headaches approximately twice a week, but no other analgesics. She denied any recent illnesses or infections, sore throat, exposure to tuberculosis, recent or present use of medications or illicit drugs, exposure to toxins, diabetes, renal problems, recent pregnancy, weight loss, joint pain, or skin rash. Family history was negative for similar illnesses or sickle cell disease. Physical exam revealed a normotensive young woman in no acute distress, with ascites, moderate facial edema, 3 mm pitting pretibial edema, and a grade II/VI non-radiating systolic ejection murmur heard best at the apex. The remainder of her exam was normal. A urine specimen obtained by catheterization showed pH, 7; specific gravity, 1.020; 3+ protein; 1 WBC; 0 RBC; 1+ ketones; 3-4 hyaline casts per high power field. A urine culture showed no growth. Her serum creatinine had increased to 1.8 mg/dl and BUN was 23 mg/dl.

On April 23, two days before admission, her serum cholesterol was 390 mg/dl (normal 120-250); total protein, 4.3 g/dl (6.0-8.0); albumin, 1.9 g/dl (3.5-5.0); serum creatinine, 1.9; and BUN, 30. We worried about lupus nephritis but fluorescent anti-nuclear antibody assay was normal, Westergren sedimentation rate was not elevated, and serum complement levels (CH50) were normal. A chest X-ray was normal. Importantly, a 24-hour urine collection amounted to only 266 ml but contained 9.0 g of protein (normal is less than 0.01 g) and 866 mg of creatinine (the predicted normal value for this patient is 700-1300 mg/dl). The calculated creatinine clearance was 32 ml/min. The patient was scheduled for admission for renal biopsy.

Clearly, the patient had the nephrotic syndrome (NS): "the clinical expression of any glomerular lesion that produces massive proteinuria (more than 3 grams of protein excreted in the urine per day)."[2] Typically, NS is characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia and edema.[3] In addition, the patient had evidence of renal functional impairment reflected by her increasing serum creatinine. She was hospitalized on April 25, and she underwent diagnostic renal biopsy the following day which revealed moderate mesangial proliferation.

Table 1
Approaching the Patient with Nephrotic Syndrome

Nephrotic Syndrome	
Secondary Causes*	**Primary Causes†**
infection	minimal change disease
multisystemic disease	mesangial proliferation
heredofamilial disorders	focal glomerulosclerosis
neoplasia	membranous glomerulopathies
toxins	membranoproliferative glomerulonephritis
	chronic nonspecific glomerulonephritis

* See table 2.
† Also known as Idiopathic Nephrotic Syndrome.

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The causes of NS are myriad. When evaluating a patient with NS (table 1) it is helpful to try to distinguish whether it is "secondary" to another disease process, or "primary" (that is, idiopathic). Sources that lead to secondary nephrotic syndrome should be ruled out first and include post-infectious sequelae, multisystemic diseases such as diabetes or lupus; heredofamilial diseases like sickle cell anemia; neoplasms; and toxins such as gold or penicillamine. A partial list of specific causes of secondary NS is found in table 2.[4]

As in the patient being discussed, if there is no evidence for secondary NS in an adult, renal biopsy can be performed to classify the type of primary NS based on histologic findings. Primary NS in the adult results from minimal change disease (15-20% of cases), mesangial proliferation (5-10%), focal glomerular sclerosis (10%), idiopathic membranous glomerulopathy (30-40%), membranoproliferative glomerulonephritis (less than 10%) or chronic nonspecific glomerulonephritis (5-10%). In many instances a histologic diagnosis can aid in both determining the patient's prognosis and establishing the most effective treatment plan; this information can not be reliably predicted from the patient's urine sediment or clinical course. A histologic diagnosis suggests which patients will respond to glucocorticoids. For example, glucocorticoids tend to be palliative in minimal change disease or membranous glomerulonephritis, but seem to have little beneficial effect in focal glomerular sclerosis or membranoproliferative glomerulonephritis.[3]

Table 2
Some of the Secondary Causes of the Nephrotic Syndrome[4]

Infections
Poststreptococcal glomerulonephritis
Endocarditis
Syphilis
Tuberculosis
Malaria
Hepatitis B
Cytomegalovirus
Infectious mononucleosis
Herpes zoster

Multisystemic disease
Amyloid
Diabetes mellitus
Goodpasture syndrome
Myxedema
Rheumatoid arthritis
Sarcoidosis
Systemic lupus erythematosus

Heredofamilial disorders
Alport syndrome
Nail-patella syndrome
Sickle cell disease

Neoplasia
Solid tumors
Hodgkin's disease
Chronic lymphatic leukemia
Multiple myeloma

Toxins
Gold
Heroin, street
Mercury
Probenicid
Tolbutamide
Trimethadione
Penicillamine

Others
Allergens (bee, snake, poison ivy/oak)
Accelerated hypertension
Congestive heart failure
Obesity
Pregnancy
Transplant rejection

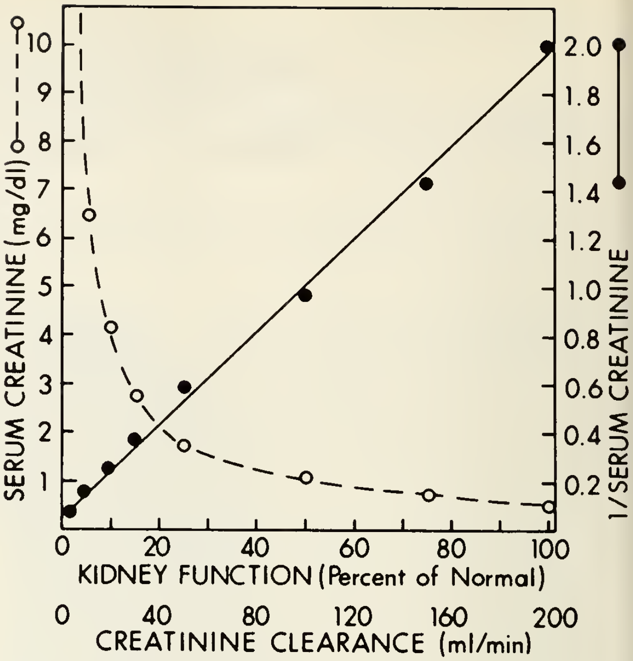

Figure 1. *The relation between serum creatinine (broken line) and kidney function. As kidney function declines, the serum creatinine rises in a nonlinear fashion. On the other hand, the inverse of the serum creatinine (solid line) shows a direct and linear relation to kidney function, declining by half its value each time the kidney function declines by half. (Data derived from Doolan, Alpen and Thail.[6])*

It was clear that the patient's renal function was declining rapidly, but the *rate* of the decline was not directly obvious from the measurement of serum creatinine alone. It is helpful to remember that serum creatinine is curvilinearly related to renal function (figure 1) as measured by either glomerular filtration rate or creatinine clearance.[5, 6] In fact, the curve shown is a rectangular hyperbola following the equation:

$$\text{Kidney Function} = 1/\text{Serum Creatinine}$$

Thus, the inverse of the serum creatinine (1/Scr) provides a *direct* estimate of kidney function (figure 1). Although the precise value of glomerular function in any given patient requires calculation of the creatinine clearance (which in turn requires collection of a timed urine specimen), 1/Scr can be used to *follow* patients with changing glomerular filtration rates.[6]

In order to get a picture of our patient's renal function, we plotted the inverse of her serum creatinines against time (figure 2) in the manner suggested by Mitch et al.[7] In a

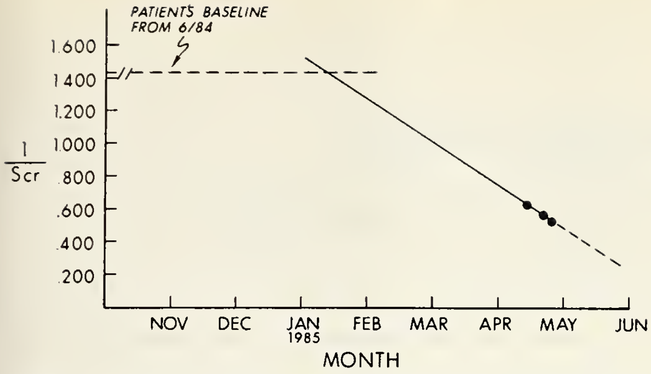

Figure 2. *Changes in the patient's inverse serum creatinine (1/Scr) show a rapid and linear decrease with time. Extrapolation of the line backwards allows us to estimate that her disease began sometime in January; extrapolation forward predicts that, in the absence of treatment, the serum creatinine would have been 10 mg/dl by July.*

study of 34 patients with chronic renal insufficiency caused by various diseases, these authors showed "that in most cases reciprocal serum-creatinine declines linearly with time as renal failure progresses."[7] In addition, "analysis of this relation in individual patients gives an estimate of the [rate of] progression of the disease, may help to determine the effects of therapy, and could be used to predict when dialysis will become necessary."[7] We were fortunate to have available a serum creatinine value of 0.7 mg/dl obtained when the patient underwent an elective septoplasty in June of 1984, and we assumed that to be the patient's baseline value. Figure 2 shows a striking linear decline in renal function. We extrapolated the line backwards to get an indication of when the process causing the nephrotic syndrome might have begun; the extrapolated line intercepts the patient's baseline sometimes in early January, about three months before the onset of her symptoms. We carefully questioned the patient about illnesses and medications during early January. Unfortunately, she could not provide any additional information. Nonetheless, the graph as well as urinary protein excretion will be useful tools with which to follow this patient's response to treatment.

Progressive renal failure presents a challenge in diagnosis and treatment. By plotting the inverse of serial serum creatinine values versus time, the clinician can monitor the progression of the disease and the impact of any treatments.

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Acknowledgment

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Purpura Fulminans Associated with *Haemophilus Influenzae* Type B Infection

John Peter Santamaria, M.D., Shannon Kenney, M.D. and Alan D. Stiles, M.D.

- *Three fatal cases demonstrate the importance of prevention. Guidelines for vaccination of young children are given.*

PURPURA fulminans is a disorder characterized by progressive, symmetrical purpuric lesions of the skin in addition to laboratory evidence of disseminated intravascular coagulation (DIC).[1] This disorder has been associated with bacterial diseases caused by streptococcus, meningococcus, and *Branhamella catarrhalis*, as well as the exanthematous viral illnesses of varicella and measles.[2-5] *Haemophilus influenzae* infections have been described with petechiae or reddish-purple cellulitis but not with the pathognomonic features of purpura fulminans.

Since the presence of this serious complication may suggest other etiologic associations and inappropriately narrow treatment regimens, the purpose of this paper is to present three illustrative cases treated on our service in a six-month period. The deaths of all three patients attest to the severity of this problem. The need for adequate preventive measures and rapid and intensive therapy is clear.

Case 1

DE, a 9-month-old white boy, presented at another hospital obtunded, convulsing, and cyanotic. Initial physical examination was remarkable for hypotension, fever, unresponsiveness, a tense fontanelle and right otitis media. A lumbar puncture revealed purulent cerebrospinal fluid (CSF) which later grew *Haemophilus influenzae* type b, sensitive to ampicillin. His coagulation profile on presentation included the following: Prothrombin time (PT), 21 seconds (control, 11 seconds); partial thromboplastin time (PTT), 108 seconds (control, 32 seconds); fibrinogen 170 mg/dl (normal, 170-420 mg/dl); and platelet count 40,000/ml.

The patient was treated with intravenous ampicillin and chloramphenicol, fresh frozen plasma, platelets, and vitamin K. Within several hours he developed marked purpura of all fingers and toes with no palpable pulses in the distal extremities. Repeat coagulation values were PTT of over 200 seconds (control, 56 seconds) and thrombin clotting time (TCT) of 34 seconds (control, 12.1 seconds). A heparin infusion (50 units/kg loading dose followed by 15 units/kg/hr) was added to his therapy with no clinical improvement. The heparin was discontinued when the patient developed massive hematemesis. He died three days after his initial presentation with uncontrollable increase in intracranial pressure and hypotension.

Autopsy revealed purulent leptomeningitis, multiple hemorrhagic infarcts of the brain with cerebral herniation, bilateral adrenal cortical hemorrhage, and multiple hemorrhagic foci in the lungs, bladder and stomach. There was purpura grossly of the hands, feet and calves. Microscopic exam of the skin from the involved regions showed marked vascular congestion and occlusion of the small capillaries with hyaline thrombi.

Case 2

SC was a previously well, 5½-month-old white girl admitted to a local hospital with meningitis which was later shown by CSF culture to be due to *Haemophilus influenzae* type b, sensitive to ampicillin. She was initially treated with ampicillin, but developed generalized seizure activity and acidosis on the day of admission and was transferred to the North Carolina Memorial Hospital. Physical exam was notable for generalized seizures, bulging, tense fontanelle, and diffuse purpuric lesions over the distal extremities symmetrically. Initial laboratory tests included the following: PT, 17.1 seconds (control, 11.4 seconds); PTT, 123.5 (control, 54.8 seconds); TCT, 13.5 seconds (control, 11.9 seconds); fibrinogen 28.1 mg/dl; Factor VIII 35% of normal, and a platelet count of 21,000/ml. The child was maintained on mechanical ventilation and measures to control intracranial pressure were instituted.

On the second hospital day purpura progressed despite vitamin K, multiple platelet and fresh frozen plasma infusions, and laboratory evidence of coagulation improvement with PT of 13.8 seconds (control, 10.7 seconds). Heparin therapy was begun (50 units/kg loading dose, then 15-20 units/kg/hr infusion) with subsequent improvement in distal perfusion and some regression of purpura. The patient's activated PTT became equal to control, but the platelet count could not be maintained greater than 20,000/ml. On the fourth hospital day a massive pneumothorax occurred and the child died. Autopsy was denied.

Case 3

PP, a 13-month-old white boy, was admitted to a local hospital with a diagnosis of meningitis. His blood and CSF cultures grew *Haemophilus influenzae* type b, sensitive to ampicillin. Laboratory tests on admission revealed PT, 16

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seconds (control, 11 seconds) and PTT, 71 seconds (control, 34 seconds). Treatment included ampicillin, chloramphenicol, whole blood, and fresh frozen plasma. There was transient clinical improvement, then deterioration including seizure activity and cardiopulmonary arrest. Coagulation indices were essentially unchanged. After stabilization he was transferred to the North Carolina Memorial Hospital.

Admission physical exam was notable for mottled skin with symmetrically distributed petechiae on the trunk and extremities, ecchymoses on both ears, and cool extremities. Neurological exam revealed sluggishly reactive pupils and bilateral papilledema. At that time laboratory values included PT of 18.9 seconds (control, 12.7 seconds), PTT of 85.4 seconds (control, 54.9 seconds) and platelet count of 7,000/ml.

Attempts were made to control the progression of purpura with platelets, fresh frozen plasma and a constant infusion of heparin (50 units/kg loading dose, then 15-20 units/kg/hr). Throughout the first hospital day there was no extension of purpura and some healing of older lesions was seen. Coagulation studies were also improved: PT 12.7 seconds (control, 11.9 seconds) and PTT 58.1 seconds (control, 34.8 seconds). On the second hospital day his ICP became markedly elevated and neurologic status deteriorated. On the third hospital day he suffered a cardiac arrest and died. No autopsy was performed.

Discussion

Each case had clinical and laboratory evidence of purpura fulminans associated with *Haemophilus influenzae* type b, ampicillin-sensitive meningitis. In two children the coagulopathy was satisfactorily controlled with supportive measures for disseminated intravascular coagulation and continuous heparin infusion. Since the coagulopathy could not be implicated as the immediate cause of death in any of the patients, these cases support the impression that heparin is useful for control of DIC in purpura fulminans although its benefit for DIC in general remains controversial.[6, 7]

The clinical course in these children was more rapidly progressive than is usually seen with this organism. It is important that the practitioner faced with a case of childhood meningitis associated with purpura not assume that *Neisseria meningitidis* is the etiologic agent. Broad spectrum antibiotic therapy, including coverage for *Haemophilus influenzae* type b as well as the more common etiologic agent *Neisseria meningitidis,* should be instituted immediately. Penicillin or ampicillin, in addition to chloramphenicol, would be an appropriate choice to cover increasing numbers of ampicillin-resistant *Haemophilus influenzae*. Awareness of the association between *Haemophilus influenzae* type b infections and purpura fulminans may allow earlier recognition of this complication and institution of heparin therapy. This may aid in the control of the coagulopathy as well as the prevention of long-term deformation associated with vascular occlusion in the extremities and facial appendages of survivors.

The failure of known intensive care therapies to alter the clinical outcome of these three patients is sobering. "Prevention first" is a medical doctrine nowhere more applicable than here.

Table 1
CDC Recommendations for Vaccination

	< 18 Months	18-24 Months	24 Months	> 24 Months
Vaccination	No	Unclear[1]	Yes	Unclear[3]
Revaccination	No	Unclear[2]	No	No

Adapted from Morbidity and Mortality Weekly Report (Centers for Disease Control), 34(15), April 19, 1985.

[1] May be considered, especially in high risk groups such as children with sickle cell disease, asplenia, malignancies, other immunosuppressive diseases, or those in day care.

[2] Second dose of vaccine within 18 months after first dose may ensure protection.

[3] May be considered, based on age-related incidence of disease and co-existence of other high risk state.

Recently a vaccine of the purified capsular polysaccharide of *Hemophilus influenzae* type b (Hib) has been licensed in the United States. The antibody response induced is inversely proportional to the age of the small child. Although there are remaining questions regarding the precise protective level of antibody, a Finnish field trial correlated levels of capsular antibody greater than 1 μg/ml in three-week postimmunization serum samples with clinical protection for a minimum of 1½ years. After a single vaccination, this level was achieved in 90% of 24-35 month-old children and 75% of 18-23 month-old children.[8] Combining these data with age-related incidence of invasive Hib disease has led to the current Centers for Disease Control recommendations (table 1).[9]

Concurrent administration of Hib and DPT vaccines at separate sites can be given without effect on the immune response to the individual antigens or adverse reactions beyond those experienced with separate administration. Side effects have not been of significant consequence to alter these recommendations.

Acknowledgment

We wish to express our appreciation to Dr. Campbell McMillan and Dr. Wallace Clyde for their advice concerning this report.

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Play It Again, Voltaire — Aconite (Monkshood) Poisoning

Ronald B. Mack, M.D.

SURELY you remember good old Voltaire. What a stand-up guy he was!! This very provocative French author and philosopher was a hero of the Enlightenment and in my opinion was one of the really good things about that period of history. His writing was prodigious but many people remember him best for his famous pronouncement: "I may disagree with what you say, but I will fight to my death your right to say it." I thought of Voltaire's statement recently when an unsolicited journal came to me in the mail and I began to experience intellectual dysrrhythmia as a result. No, I'm not talking about the "journals" I receive in brown paper wrappers — I like those — the interviews are simply marvelous.

The name of the journal that caused me to dissemble is *American Homeopathy,* Vol 2, Number 3, March 1985, published by the United States Homeopathic Association. On page 4 there is an article entitled "Comparison of homeopathic medicines for treating tonsillitis." The article discusses this disease and then states "If the condition is ascertained very quickly, a dose or two of Aconite has an excellent chance of aborting tonsillitis." When I read the word *aconite* I stopped reading for a moment and gulped. Aconite was known to the ancient Greeks as an excellent poison. Medea, of Greek mythology fame, was a very tough lady. She was deserted by her husband, Jason (of the Golden Fleece); he found a younger woman to dally with (Excuse me, dally? Is that a euphemism for ________? Never mind!!). Medea was very angry and murdered all of her children by Jason except one. She then married Aegeus, King of Athens. Aegeus had a son, Theseus, whom Medea tried to kill with aconite but she failed. William Shakespeare knew plenty about this potentially deadly plant. In *Henry IV,* part 2 King Henry himself says ". . . though it does work as strong as aconitum. . . ." In this passage (Act IV, Scene IV) the King speaks to his sons concerning the strength of the love between brothers and says it must be so strong as to resist the force of a poison as strong as aconite or of gunpowder. This plant has been considered so poisonous and powerful throughout history that it was used extensively to coat arrows and daggers. In *Hamlet,* Laertes says "And for that purpose I'll anoint my sword. I bought an unction of a mountebank so mortal that but dip a knife in it, where it draws blood, no cataplasm so rare . . . can save the thing from death that is but scratched withal." Hamlet dies within "half an hour" after being poisoned thus and laments before dying, "Oh, I die, Horatio, the potent poison quite o'ercrows my spirit."

Just what is this plant that has been so popular for millennia!! Is it still around? You bet your bippy it is!! Aconite has many synonyms, e.g., it is probably better known these days as *Monkshood* but it is AKA Friar's Cap, Helmet Flower, Soldier's Cap and the ever popular Wolfsbane. There are 100 species of this plant that are native to the north temperate zone and they grow in cultivated flower gardens and in the wild throughout most of the United States and Canada except in the so-called "deep South." The Monkshoods are perennial plants, mostly erect, sometimes branched, about two to six feet in height. The characteristic upper part of the plant is like a hood (no, not like the guys who grow up in my old neighborhood, but like a cap or cowl) reflected in the various aliases that this flora enjoys — Friars Cap, Soldier's Cap, etc. The flowers of most of the species are blue but can be pink, white or flesh toned. The seed pods contain numerous small seeds.

Probably the entire plant should be considered poisonous. The leaves, roots and seeds are particularly troublesome if ingested (or if you happened to be hit by an arrow or stabbed with a dagger immersed in the plant's contents) because they contain *aconitine* and other poisonous alkaloids such as delphinine and ajacine. These chemicals are polycyclic diterpenoid alkaloids (of course they are!! I knew that!!). Aconitine has been used experimentally by medical researchers to disrupt the normal heartbeat so that new drugs that affect the heart can be evaluated.

Gosh, I wonder what happens when you receive some unwanted aconite!! The alkaloids are alleged to be so toxic that merely picking the flowers of this plant can cause prickling and/or numbness of the fingers. Poisoning does occur, by ingestion usually — accidentally, of course — or by eating the leaves as salad greens or by having it prescribed by uh, uh, uh practitioners. The symptoms of this plant poisoning develop quite rapidly, usually within 30 minutes of ingestion, and are experienced initially as a numbness or burning feeling of the entire oral mucosa, lips and throat which may ultimately involve the entire dermal surface including the extremities. Speech, of course, may be difficult and this is often followed by salivation, nausea and vomiting, abdominal pain that is crampy in nature and diarrhea. Gastrointestinal distress seems to be the most common denominator in a typical plant poisoning regard-

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From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

less of species. Within limits this is not necessarily a terribly destructive adverse effect as it helps to rid the body of the plant parts and any unabsorbed toxins. Visual blurring can develop with yellow-green vision (as in oleander, fox glove, star-of-bethlehem poisonings) with *mydriasis*. At this point the patient is dizzy, weak, uncoordinated and, if able to speak, complaining of paresthesias, muscle cramps, and generalized body pain. The worst is yet to come!! Monkshood alkaloids first stimulate then depress both central and peripheral sensory nerves. The effects on the heart are similar to quinidine. In the worst scenario, cardiac rhythm disturbances can lead to cardiac or respiratory failure in as little as 5 minutes or as long as four days. The lethal dose is approximately 5 mg of the alkaloid or a teaspoonful of the root; needless to say it is hard to standardize this substance.

So, you ask, just who are these people — the homeopaths — who, within a few years of the 21st Century, recommend this substance, allegedly, for acute tonsillitis as well as decreasing "heart action," decreasing elevated blood pressure, treating neuralgias, antipyresis, reducing rheumatic pains, etc. Our story goes back to the father of homeopathy, the German physician and theorist, Samuel C. Hahnemann (1755-1843) who was apparently rebelling against the so-called "orthodox" medical system of the day which often consisted of what came to be known as Heroic Medicine, e.g., bleeding, purging, cupping, blistering and sweating (wouldn't Galen have been proud that his teachings from the First Century A.D. were still popular in the 18th and 19th Centuries?). Hahnemann, who had conventional medical training, formulated at the end of the 18th Century the fundamental law of homeopathy: similas, similibus, curantur ("like may be cured by like").[1] In an explanatory brochure published under the auspices of the U.S. Homeopathic Association, it is stated, "The science of homeopathy rests on the principle that illnesses result from natural causes, and that substances — animal, vegetable, mineral and chemical — when given in large doses to a healthy person will cause known illness-like reactions. In homeopathy, an illness is treated by giving the patient minute doses of a substance or substances that produce a set of symptoms identical to that of the illness." (Well, so much for that — res ipsa loquitur. Keep quiet, Mack — play it again, Voltaire!!)

The treatment of Monkshood AKA aconite poisoning is, as you have guessed, symptomatic. Ingestion of any amount of this quite toxic compound should probably require you to administer ipecac syrup rather promptly (unless the condition of the patient contraindicates this emetic) followed by activated charcoal and a saline cathartic. It is probably wise to observe the patient via monitors, etc. for cardiac or respiratory depression. More specific treatment is directed toward the management of cardiac arrhythmias should they occur. Apparently bradycardia is quite common in this poisoning and thus atropine assumes the role of the drug of choice if such an adverse effect occurs.

This is the 40th Anniversary of the end of WWII. As ludicrous as it seems to me now, I can recall vividly my treatment for the sore throats incurred by my fellow shipmates. In my role as a Pharmacist's Mate Third Class on a supply ship in the Pacific I followed the Navy's instructions and painted their throats with merthiolate (Oh Hippocrates, please forgive me!!).

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Thirst, Dehydration, and Old Age

William B. Blythe, M.D.

- *The elderly may need more water than they think they need.*

As both seasoned physician and October intern unfortunately know too well, dehydration is more dangerous and much more common in the elderly patient than in younger adults. Why?

The increased hazard of dehydration in the older group is due to blunting of the cardiovascular reflexes which respond to, and minimize the effects of, depletion of the plasma volume. Thus, for a given loss in plasma volume, the older patient is more apt to develop symptoms of orthostatic hypotension and evidence of hypoperfusion of virtually all organ systems.

The higher prevalence of dehydration in the elderly is usually ascribed to a combination of two factors. First, the aging kidney is unable to concentrate urine as well as the younger one. Thus, for a given degree of water deprivation, the older patient is more apt to sustain a greater loss of plasma volume than a younger one. The only means by which dehydration can be naturally corrected is by an increased intake of fluid occasioned by thirst; and thus the need for the second factor to explain the frequency of dehydration in older people. The traditional view has been that, as a consequence of the sluggish cardiovascular response to dehydration or to illness *per se*, diminished mental awareness and confusion develop, thirst is abolished or decreased and dehydration thereby begets further dehydration.

Thus, in this construct, at least some slightening of mental acuity is necessary for diminished thirst.

A recent important study suggests that even the latter is not essential and makes it even clearer as to why dehydration is so common in the elderly. Investigators in Oxford, England studied the effect of water deprivation for 24 hours on thirst sensation in a group of healthy, elderly men and a control group of healthy, young men. After the period of water deprivation, both groups were asked to rate the degree of thirst occasioned by the water deprivation and then, during the following hour, to drink the amount of water needed to assuage their thirst.

The results are fascinating. Despite the fact that the stimuli for thirst were stronger in the older men, they were less thirsty and drank significantly less water during the repletion period than did the younger men.

Those who care for the elderly take heed! Fluid losses via mild gastrointestinal illness or modest diuretic therapy may not invoke thirst in this group and dehydration and plasma volume deficits may progress to a dangerous degree, even though there is no change in mental acuity. There may be times in the nursing home or hospital when water should be prescribed! It is cheaper and may save more lives than expensive and fancier nostrums.

From the Department of Medicine, UNC, Chapel Hill 27514.

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1. Phillips PA, Rolls BJ, Ledingham JGG, et al. Reduced thirst after water deprivation in healthy elderly men. N Engl J Med 1984;311:753-9.

It has come to the attention of the Board of Medical Examiners that there are a growing number of situations in North Carolina in which ophthalmologists have entered into arrangements with optometrists whereby the optometrists refer to the ophthalmologists patients for cataract surgery and that following such surgery these patients are then returned by the ophthalmologists to the care of the referring optometrists for postoperative care and following. Because it is the view of the Board that such postoperative care and following constitutes the practice of medicine, the practice of permitting persons who are not licensed to practice medicine in the State of North Carolina to provide such care is specifically disapproved by the Board.

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

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PROFESSIONAL USE INFORMATION

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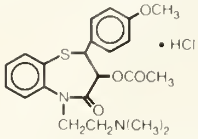
DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina. CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted.

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

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Peritonitis in a Patient on Continuous Ambulatory Peritoneal Dialysis

Debra A. Heldman, M.D.

- *Report of a case of peritonitis caused by the fungus Fusarium oxysporum.*

OVER the past decade, continuous ambulatory peritoneal dialysis (CAPD) has become an accepted and increasingly utilized method of treating patients with chronic renal failure. Its advantages over hemodialysis include lower cost, increased patient mobility, higher hemoglobin concentration, fewer fluid and electrolyte restrictions, better biochemical balance, and better control of blood pressure.

The most frequent serious complication of CAPD is peritonitis which occurs every year or two in the average patient. Vas et al[1] require at least two of the following three criteria to establish a diagnosis of peritonitis: 1) abdominal pain or tenderness, 2) peritoneal fluid with greater than 100 neutrophils/mm^3, and 3) organisms in the peritoneal fluid. Gram positive organisms (usually Staphylococcus epidermidis, Staph. aureus, or Streptococcus) cause 60-70% of cases and gram negative organisms (usually E. coli, Pseudomonas, Klebsiella, or Enterobacter) cause 15-30%.[1-3] The remaining cases are caused by anaerobes, less common bacterial species, or fungi.

I recently cared for a patient on CAPD who had peritonitis due to an unusual organism. This patient was a 41-year-old black woman with chronic renal failure who had been on CAPD for three years. Two weeks before admission to our hospital, she developed diffuse abdominal pain, nausea, vomiting, and low-grade fever. When she initially developed these symptoms, she was admitted to another hospital and felt to have bacterial peritonitis. She was treated for three days with intraperitoneal cephalothin but her peritoneal fluid showed fewer than 100 neutrophils/mm^3 and cultures were negative. Her symptoms did not improve and she came to us for another opinion. Her temperature was 37.5° C and she had bilateral lower quadrant tenderness. The peripheral white blood cell count was 14,300; the peritoneal fluid had 47 white cells/mm^3 with 49% neutrophils. An abdominal echogram showed small kidneys; there was no perinephric fluid collection or evidence of loculation elsewhere. She was admitted to our hospital and was treated empirically with intravenous and intraperitoneal tobramycin. This was discontinued on the third hospital day when peritoneal, blood, and urine cultures were negative. Subsequently, the peritoneal fluid grew a fungus identified as Fusarium oxysporum. (See figures 1 and 2.)

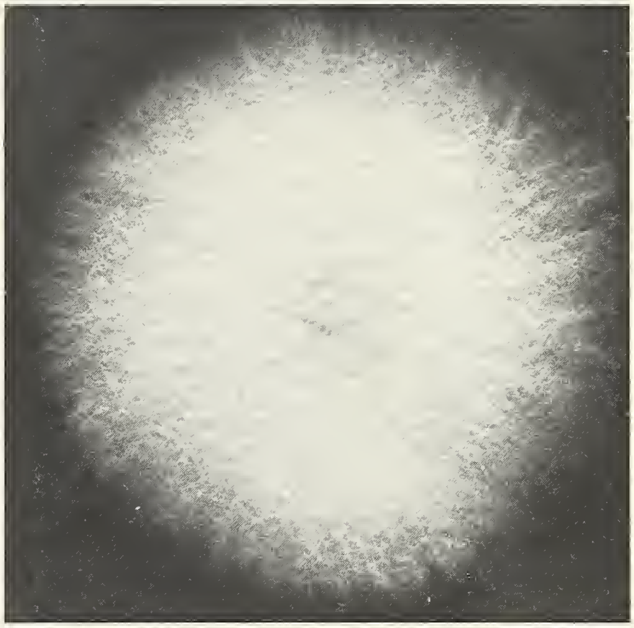

Figure 1. *Fusarium oxysporum growing on agar.*

Fusarium is a mold found in the soil and air throughout the United States, especially in the Southeast. Human infections with Fusarium are uncommon but have been described in keratitis, endophthalmitis, burn infections, brain abscess, osteomyelitis, skin infections, septic arthritis, and disseminated opportunistic infection.

Three cases of peritonitis caused by Fusarium have been reported previously, all in patients on CAPD.[4, 5] Fusarium is or rapidly becomes resistant to antifungal agents.[4, 6] McNeely et al[4] described two cases of Fusarium peritonitis, one caused by F. moniliforme, the other by F. oxysporum. In both cases, the organism had or developed resistance to amphotericin, 5-fluorocytosine, and miconazole. Kerr et al[5] described one case of peritonitis caused by a Fusarium species on which sensitivity testing was not done. In addition to being resistant to antifungal agents, Fusarium has been shown to adhere to and invade the wall of the peritoneal catheter of a patient.[4] Both of these factors are important considerations in determining the appropriate therapy for Fusarium peritonitis.[4] McNeely et al[4] treated

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From the Department of Medicine, Duke University Medical Center, Durham 27710.

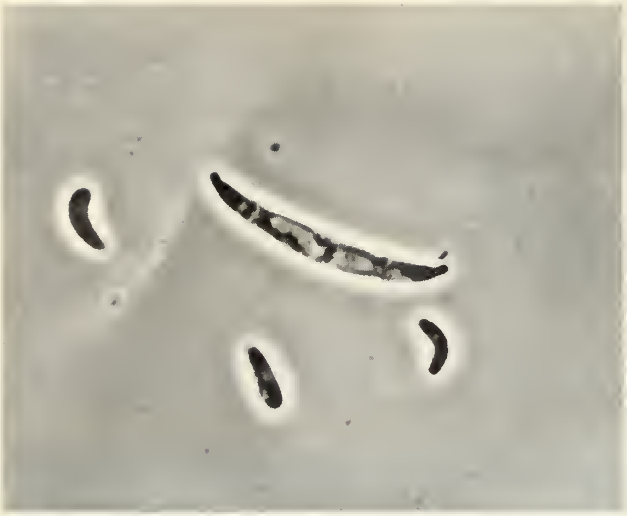

Figure 2. *F. oxysporum spores on lactophenol slide, unstained, magnification × 1300.*

the first of their patients with miconazole intraperitoneally for 21 days during which time the peritoneal cultures remained positive for Fusarium. After removal of the section of peritoneal catheter harboring a Fusarium "vegetation," the cultures became negative. They successfully treated their second patient with catheter removal only. Kerr et al treated their patient with Fusarium peritonitis with I.V. amphotericin and catheter removal.[5]

Since these three previously described cases showed little or no benefit from antifungal drugs, we elected to treat our patient just by removing the Tenckhoff catheter. Cultures of the catheter tip and subcutaneous cuff were positive for Fusarium oxysporum. After catheter removal, the patient did well with resolution of her symptoms. She was hemodialyzed for three weeks after which the catheter was replaced. She has continued to do well three months after catheter replacement.

Fusarium is one of several fungi that can cause peritonitis in patients on CAPD. Five to fifteen percent of all cases of peritonitis in these patients are caused by a fungal organism.[3, 5, 7] In addition to Fusarium, these organisms have included Candida albicans, Candida paraspilosis, Candida tropicalis, Torulopsis glubrata, Trichoderma viride, Exophiala jeanselmei, Drechslera spicifera, Drechslera australiensis, Mucor sp., Trichosporum sp., Rhodotorula rubra, and Aspergillus fumigatus. Most cases have been secondary to Candida with only a few cases caused by other species.

Thus, CAPD represents a major advance in our ability to treat chronic renal failure. An appreciation of the risk of peritonitis and the organisms that cause it is necessary for successful use of this form of dialysis. Symptoms of fungal peritonitis mimic those of the more common bacterial peritonitis (abdominal pain, fever, and cloudy peritoneal fluid with increased neutrophils). The management of fungal peritonitis is controversial. Some favor early catheter removal in all cases. However, others have reported successful treatment of sensitive organisms with appropriate intraperitoneal (with or without intravenous) antifungal therapy.

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The Entrepreneur Physician

William L. Trombetta, J.D., Ph.D. and Leif C. Beck, J.D., C.P.B.C.

> *There are the few who make things happen, the many more who watch things happen, and the vast majority who say — "what happened?"*
> *Nicholas Murray Butler*

IN our work with medical practices, we have begun to notice a most interesting phenomenon. While performing a marketing study here, a one-shot consulting assignment there or dealing with arrangements for a satellite office building, we are also witnessing the emergence of the "entrepreneur physician." This is the type of doctor who takes risks to start a new venture, succeeds in getting it up and running despite various odds against success and yet hopefully manages to keep his or her marriage, family life and ideals relatively intact in the process.

A Special Breed

The entrepreneur physician appears to be a special breed apart. At one time or another, almost everyone has had an idea that would certainly make a million dollars if properly carried out. Yet very few of these "ideas in the shower" ever come to fruition. The entrepreneur physician, however, has the special abilities to spot and evaluate business potential and, most importantly, to implement those opportunities into something significant.

Another interesting characteristic of entrepreneur physicians is that, demographically, they are indistinguishable. They come in all ages and medical specialties. But there is something in the entrepreneur physician's psyche not easily measurable and virtually impossible to quantify — call it motivation, drive, desire or hunger — that sets him or her apart.

Formal business education and extensive business experience do not seem to be necessary. This parallels the business world in general where many successful entrepreneurs have no MBA degree or comparable background. We remember, for example, a pediatrician who is the heart and soul of a thriving large multi-specialty group practice though he came into this role simply by his willingness to assume responsibility and to be alert to the group's opportunities and challenges.

Entrepreneur physicians depart from many business-world entrepreneurs in one respect, though. Those with whom we have worked are neither rebels, outcasts or mavericks as are many other successful businessmen; rather, they are doctors who remain successful in their more conventional careers as physicians and who continue to insist on high standards of quality health care. One general internist in New York state, for example, still maintains the heaviest, loyal patient following while leading his ten-member group into arrangements which we think will cause growth to 25 or more doctors in just a few years; quality has in no way been compromised in his efforts.

Not Satisfied

In addition to being risk takers and innovators, entrepreneur physicians are not satisfied with the status quo. They anticipate and initiate change rather than passively react to market forces. This conforms with one of our key sayings for forward-thinking physicians these days: "The best way to manage in an environment of escalating change is to anticipate change."

Though not always the case, many of the entrepreneurial physicians seem to be more comfortable starting up new enterprises instead of merely operating and managing existing practices. As a corollary, many of them are not oriented toward administration. This is significant because as a professional enterprise matures, what may have started as a special challenge inexorably shifts to an administrative and executive phase in which planning, pricing, marketing and financing become far more important than "the creative juices."

There is, for example, a highly successful solo specialist who is moving from that one-doctor configuration to what should be a regional center for his specialty comprising many doctors and unique features. In making the transition, we have identified the need for converting his developmental and medical talents into the disciplined approach of a true executive as being vital to his project's future. This would represent the conversion of his entrepreneurial capacity into an ongoing business/professional success.

Reinvigoration

Entrepreneurs constantly focus on periodic themes to keep reinvigorating themselves. One group practice which we place in this category meets frequently to assess the relationship between its recently adopted lower fee schedule (which was a competitive strategy) and the quality of its services. These doctors realized at the outset that no one, including third party payors, is interested in "the lowest prices in town" but rather in the best value for the dollar.

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Hence, they periodically challenge themselves to do more in the way of providing "value added" health care services to their patients while keeping their fees below those of most of their peers.

Another group practice in its initial formative stage of association has created a working committee whose sole assignment is to critically evaluate alternative delivery systems. It is particularly on the lookout for where the "blind-side competition" will be coming from. The committee members play devil's advocates in projecting how, if they were various other competing providers, they would attempt to compete with their own entity.

Alert to Competitors

And a family practice group we know of meets regularly to discuss and hopefully discover competitive approaches of which their "colleagues" (who really are their competitors in the same service area) either are unaware or are ignoring. This group's forum is an informal "rap" session during which the doctors attempt, among other things, to list as many consumer concerns as possible for the kinds of health services they provide. In other words, their orientation is not what services the doctors provide (a "product" orientation) but what benefits their patients derive (a "consumer" orientation).

This kind of brainstorming led the family practice group to begin marketing a "health well-being education" service to people who purchase home health care kits in the emerging self-care market. The doctors believe they can position themselves as the premier health care information source to consumers who remain apprehensive about administering and understanding self-care products after the purchase of such products.

Just as entrepreneurs who started vastly successful high-tech companies (like Wang, Apple and lesser successes), these entrepreneurially-minded family practitioners are keeping their focus on the consumer. They follow a "reinvigoration" process to be sure they stay closely enough attuned to the buyers of their services to keep their momentum going.

Risk Takers, But Adapters

Entrepreneurial physicians reflect a tension common to all risk takers — they are not that concerned over security. That is, they are personally not afraid to fail or lose their investment as part of the price for special accomplishment. Indeed, they thrive on challenge and hard work so long as they are part of something new. Family values can easily be shunted to the wayside by such people, but interestingly most of these doctors we have seen appear blessed with continued good perspectives on their whole lives.

Perhaps part of their sense of perspective, the entrepreneur doctors accept the need for thought processes that most physicians reject as not within their training. They are active in forecasting revenues and overall budgeting, in evaluating costs and capital requirements and in the hard discipline of strategic planning. One group of just four partners in a nearby state, for example, has assembled a 200-page prospectus describing the group; their avowed purpose is to attract major corporate financing for their expansion plans within the HMO, PPO, etc. environment.

Finally, entrepreneurial physicians share supportive value systems and an optimistic corporate culture. Whereas many others in medicine see only negativism and external meddling by outside forces in these turbulent times, the entrepreneurs seem to accept free enterprise and competition. They look upon the problems facing health care as opportunities to be capitalized upon in hopes that these opportunities will result in better health care and increased consumer satisfaction, while benefiting themselves and their groups.

Conclusion

Today, we live in an era of innovation and entrepreneurial drive. This fact is true in every other industry, and there is no reason to exempt health care from the patterns. As events seem to overwhelm most doctors, and in the long run we fear that events will in fact do so, entrepreneurial physicians promise to be the people who will adapt and prosper. Group practices with such people in their midst are indeed blessed, though possibly uneasy.

CONJOINT REPORT

The State of the State

Ronald H. Levine, M.D., MPH

- *Dr. Levine reviewed the health of North Carolina in this address at the Annual Meeting of the North Carolina Medical Society on May 3, 1985.*

IT is an honor to once again carry out my statutory obligation of presenting to the physicians of North Carolina as well as the members of the Health Commission a review of the major public health accomplishments of the year past. Just last week the latest results of The North Carolina Citizen Survey became available. I was struck by the finding that over a third of our adult population indicated they had one or more of the following diseases: high blood pressure, heart disease, stroke or glaucoma. Add arthritis and the percentage increases to 44%. The staggering future economic burden that faces us as a state and nation as a result of morbidity and mortality among tomorrow's aging population has led me to devote a sizable section of this discussion to the topic of health promotion efforts in North Carolina. First, however, let me review some of the achievements recently recorded, much of them with your help and support.

During the last several years the provision of health care to tuberculosis patients has changed dramatically from sanitorium-dwelling to a community-based approach. Reliance upon the 12 acute care hospitals and our local health departments, now our front line against this disease, has not compromised the control program.

We found that 41% of newly positive TB cases on treatment converted their sputum to negative within three months and that 71% had converted within six months. Eighty-three percent of patients who were started on drugs completed the prescribed course of therapy. Eighty-eight percent of close contacts of patients were examined within 14 days of when the local health department was notified.

Forty-seven percent who were on preventive therapy with INH completed the prescribed 12-month course of treatment. Although all these indices fall short of the ideal they do indicate, as does our falling incidence rate, that the closure of the sanitoria has not led to a decrease in program quality. A disturbing note is that there were two outbreaks of disease caused by drug-resistant *mycobacterium tuberculosis* in our state. One of these strains is the first ever documented to be resistant to four drugs.

In the area of sexually transmitted diseases, reported gonorrhea cases (including military morbidity) decreased for the second consecutive year. During 1984, more than one quarter million women in family planning clinics and elsewhere were screened for gonorrhea and slightly less than 5% were positive. This screening effort, coupled with referral of sex partners for examination and patient counseling and treatment, has played a large part in the reduction of this disease.

Drug resistance is a problem with this bacterium also. We saw an increase from 24 cases with penicillin-resistant strains during 1983 to 62 cases during 1984. These were reported from 15 different counties during 1984, compared with only 10 counties the previous year.

Early syphilis cases decreased for the first time in five years. Although the decrease was only 1%, this reversal of the upward trend is encouraging. We only had two cases of congenital syphilis in 1984. We should not have any!

An area of present and future concern is the AIDS problem. The acquired immunodeficiency syndrome was first described in 1981 and was quickly recognized as an almost universally fatal disease. North Carolina has reported 75 patients with the disease and 53 of those have already died.

A primary concern is that infected persons may contaminate the nation's blood supply. On March 2, the Food and Drug Administration licensed a test for blood banks to use to detect antibodies to the presumed causative agent. Blood showing a positive finding will be discarded and the donor will be informed.

The Centers for Disease Control is intent upon discouraging concerned high-risk individuals from donating blood just for the purpose of receiving a screening test at blood banks and thereby increasing the danger to the blood supply due to possible false negative tests. They have called upon us and we have agreed to set up alternative diversionary testing sites across the state. The sites will be located in most local health departments. [See NCMJ 1985;46:353-360.] The North Carolina State Laboratory will perform the screening tests and obtain confirmatory tests, if indicated, on blood specimens drawn at local health facilities. The individual will receive pretest counseling, post-test counseling if test results are positive, and referral for medical evaluation. Printed materials will be made available to assist in these counseling sessions. Personnel from the Venereal Disease Control Program will be reassigned in order to assist counties with this effort. Please do not hesitate to call or write our agency if you would like more information on this effort.

In the area of Dental Health, we continue to improve our fluoridation coverage throughout the state. The fluoride content of water supplies is being adjusted to the optimum level in 195 North Carolina communities; 26 additional towns are served by naturally fluoridated water. Thus 85% of the population served by a municipal water system is receiving fluoridated water. An additional 52,000 children

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From the Division of Health Services, Box 2091, Raleigh 27602-2091.

are served by rural school-water fluoridators, and 390,000 children in grades K-8 in over 1000 schools in 85 counties participate in a weekly sodium fluoride mouthrinse program; 80% of these children live in non-fluoridated areas. The 55% decrease in dental caries achieved in our state by the country's #1 preventive dentistry program should be readily recognizable to you when you look in your young patients' mouths.

Maternal and child care continues to be a major emphasis of your state and local public health agencies. In 1983, North Carolina's infant mortality rate was 13.2 deaths per thousand live births, down from 13.7 in 1982, but reflecting an unmistakable leveling of what had been a rather steady and significant drop in infant mortality over a considerable time. The prevention of premature births is at the core of our efforts to re-set in motion the reduction in infant mortality. As of this date 83 counties have implemented prematurity risk assessment and intervention systems. If these efforts are successful we expect to see some impact on the incidence of low birthweight beginning in 1986 or 1987. This year we completed the network of 21 regional high risk maternity clinics. Only nine counties remain that have no publicly-administered prenatal care for indigent pregnant women. Unfortunately, some of these nine are among those with the highest infant mortality rates in the state.

Teen age pregnancies remain a problem. In 1979, North Carolina ranked eleventh nationally in the percent of all live births that occurred to women 19 and under. At that time one in 13 adolescents aged 15 to 19 became pregnant. Since then this statistic has worsened. In 1983 one in eleven North Carolina teens 15-19 became pregnant. Mothers under 20 produced 21 percent of all pregnancies, 17 percent of live births, 23 percent of low weight babies and 24 percent of the neonatal deaths. Teens were less likely to begin their prenatal care early and less likely to have at least eight prenatal visits. Our Family Planning Program continues to provide clinical services to these teenagers but is also initiating programs for parents and teenagers on the subject of postponing sexual activity. Over 200 individuals in this state have been trained to use the "Postponing Sexual Involvement" curriculum developed at Emory University. Many of these trainees have in turn offered training in their communities and, in some instances, have worked with local education agencies to incorporate this into the school curriculum.

Let us turn now to more in-depth coverage of health promotion programs and services in our state. At the turn of the century the leading causes of death were infectious and communicable diseases. Gains against these once great killers came as a result of improvements in sanitation, housing and nutrition and the advent of immunizations and antibiotics. Maintaining services to prevent infectious and communicable diseases among those at risk remains an important task for public health.

Today's leading killers and cripplers are chronic diseases and accidents. New methods are needed to address these causes of death and disability. These methods unavoidably focus on lifestyle change and environmental enhancement as well as anticipatory, high-quality medical care.

To understand the need for successful preventive interventions in our state, it is useful to look at data on premature adult mortality, i.e., those deaths occurring between the ages of 18 and 64. In North Carolina each year there are approximately 49,000 deaths from all causes, one-third of which occur during this age span. Thus, 45 North Carolinians die prematurely each day. This is a tragic waste. These deaths are occurring during the "productive" years of life. In fact, in 1981 almost 200,000 person-years of the adult working population of North Carolina were lost. The economic impact of these deaths is estimated at 2.1 billion dollars.

In comparing North Carolina against the latest national data, we found that age-adjusted mortality rates for cerebrovascular disease are 27% higher in North Carolina, motor vehicle accidents 10% higher, all other accidents 17% higher and pneumonia and influenza and nephritis 10% higher. Our age-adjusted heart disease rate is almost 9% higher than the nation. In addition, cancer mortality appears to be rising faster in North Carolina than in the United States. Between 1979 and 1981, the state's age-adjusted cancer death rate rose by 2.5% while the national rate rose by .9%.

Age-adjusted mortality rates show wide gaps in the overall risk of mortality for North Carolina men versus women and nonwhites versus whites. In 1979-81, the male mortality rate was nearly double the female rate. The nonwhite age-adjusted mortality rate for both sexes remained more than 40 percent above the white rate. This suggests that preventive interventions should be targeted to specific high risk groups.

As much as 50% of mortality may relate to lifestyle. Individuals can make modest lifestyle changes which can substantially reduce risks for several of the leading causes of death. Such measures include but are not limited to:

- — reduction of alcohol misuse
- — moderate dietary changes to reduce excess intake of calories, fat, salt, and sugar
- — elimination of cigarette smoking
- — participation in periodic, targeted screening
- — adherence to speed laws and seat belt use

A growing number of intervention programs are demonstrating positive health outcomes or impacts. From these successes, certain characteristics which seem to be effective in reducing health risks have been identified.

First is the use of a reasonably formalized risk assessment to assist individuals in identifying elevated health risks. The subsequent referral of those persons who wish to make changes in their health behavior via an appropriate intervention program is more likely to lead to some measure of success.

A second characteristic is the use of periodic selective screening; let me emphasize not mass multiphasic screening but selective screening (determined by age and sex) for major disorders such as hypertension and certain forms of cancer. This type of screening is much more cost-effective and more likely to reveal significant findings that can be further clarified and diagnosed by the physician and lead to successful early intervention.

A third characteristic of successful programs has been the deliberate use of multiple interventions to address a specific health problem in a specific target population. This approach is based on an understanding that behavior is complex. Multiple causative factors are involved in the adoption of an unhealthy behavior. Thus, for many persons there is a need for multiple interventions to bring about a reversal in this behavior.

To provide an example of what is meant by multiple interventions, it may be useful to look at interventions aimed at weight management.

Some intervention methods are client oriented, for example:

- — Physician counseling about the health risks caused by obesity
- — Nutrition counseling which might be provided by the physician or by a nutritionist in the health department
- — Cooking demonstrations using recipes from *The American Heart Association Cookbook*

Other interventions may be simultaneously carried out by local groups using social support systems to bring about changes in group members. For example:

- — Weight management programs conducted in local churches
- — After-dinner walking programs sponsored by women's clubs

Yet other interventions might focus on creating an environment where healthy choices are accessible. For example:

- — Replacing traditional vending machine foods with healthy alternatives in local workplaces
- — Establishing a low calorie special in daily menus at local restaurants

The disease prevention and health promotion concepts I have described are now just beginning to be applied in a number of North Carolina sites; and it appears that there has been a rather gratifying response to these efforts among middle and upper income groups. It would not be accurate, however, to claim success among our lower income groups, at least to this point in time.

There is today a need to make disease prevention and health promotion programs operational on a wide scale throughout the state, and not just on ethical and medical grounds. If, as is estimated, our over-65 citizens in the year 2025 will number 1 out of every 4 of us and if these senior citizens of the future require abundant nursing home care and frequent hospitalization, I am afraid we will break the bank. To avoid economic consequences of great magnitude relating to our rapidly aging population, we have to see to it that 65 is young, and you know that that can be accomplished.

It is my hope that our local health departments can serve as catalysts to build strong local coalitions for disease prevention. Such coalitions should involve the medical community, business and industry, voluntary agencies and other local organizations. These groups should work jointly to identify priority disease prevention needs in communities, to develop common objectives, to develop comprehensive strategies for reaching objectives, and to develop the necessary resources. Such a comprehensive approach would help to assure that disease prevention efforts reach all segments of the community and that they have a high potential for success.

At the state level, we must give the local health departments the means to get this message across to their clients. We have recently developed a media center which will provide to health departments and other local agencies audiovisual messages that are usable with populations with low levels of literacy. We have also used federal block grant funds to initiate a series of risk reduction projects in a number of counties. The purpose is to reduce the prevalence of specific health risks in targeted populations. Projects range from implementation of worksite health promotion projects to implementation of an accident prevention program for farm workers.

We also must find the means to more adequately measure the extent of these problems in North Carolina. A risk factor surveillance system via an on-going telephone survey has begun and will provide information on the health behavior of North Carolinians related to seat belt use, high blood pressure, diet, exercise, smoking and stress. We now know that in attempting to understand the problem of cancer in the state, the higher survival rate we now thankfully experience renders the use of mortality data terribly incomplete. Thus, a recent study commissioned by the North Carolina Board of Science and Technology recommended a rejuvenated state central cancer registry supported by strong regional registries in our major medical centers. We are very optimistic that, with the strong support of your Cancer Committee, indeed the entire North Carolina Medical Society, we can bring this effort off successfully.

Now in issuing a call for a major collaborative effort to the many community organizations, the public health system, the private practitioners, the media and the general public in behalf of disease prevention and health promotion am I promising too much? Are such goals overly optimistic regarding what truly can be achieved? There are skeptics out there; probably there are several in this room. If you are on the fence, please listen and heed these unassailable findings, recently summarized in *The New England Journal of Medicine*.

First, The Numerator — The Patients

For persons aged 35-74, the death rate for coronary heart disease has fallen more than 30% since the late 1960s. Death rates from stroke have fallen even more precipitously. This decline is the greatest of any country in the world. Although better postcoronary care of patients may play some role in this, it is clear that the rate of heart attacks has decreased significantly over that period.

The Denominator — The American People

1) By 1979 almost two-thirds of all Americans had changed their eating patterns and attributed that change to health concerns.

2) The intake by American adults of eggs, fat-containing dairy products, and beef is substantially down.

3) In the early 1960s mean serum cholesterol among middle-aged men was about 240 mg/dl. The mean is now approaching 200.

4) In 1964 the majority of men smoked; now only about one-third do.

5) The decline in cardiovascular mortality has been much greater in salaried workers vs. wage employees, in higher socio-economic groups vs. lower, in physicians vs. the

general population — all attesting to the importance of the ability to understand and adapt this concept. I think you will be particularly interested in this next finding. Twenty-five years ago white male California physicians were dying from coronary heart disease at a rate 15% higher than aged-matched non-physicians. They are now dying at a rate 31% lower than the control group. Trends in mortality from lung cancer parallel these findings. It will not be a surprise for you to hear that 25 years ago a majority of male physicians were cigarette smokers. Today less than 10% of physicians smoke as compared with 40% of white men generally.

Time prevents me from exploring issues of seat belt use, sedentary life style, stress management and other health behaviors, but I submit that the jury is in, its verdict is unassailable and it is now the job of the practitioner, the university, the health department and anyone else who can lend a hand to convert this understanding into concerted, effective action.

I am confident that the strong collaborative effort that we have demonstrated in the great victories we have together won and enjoyed in the past over such enemies as communicable disease, environmental contamination and maternal mortality can and will be utilized as we intensify our efforts to reduce preventable, premature death and disability from today's major health problems.

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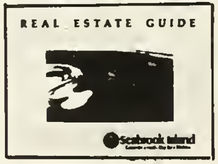

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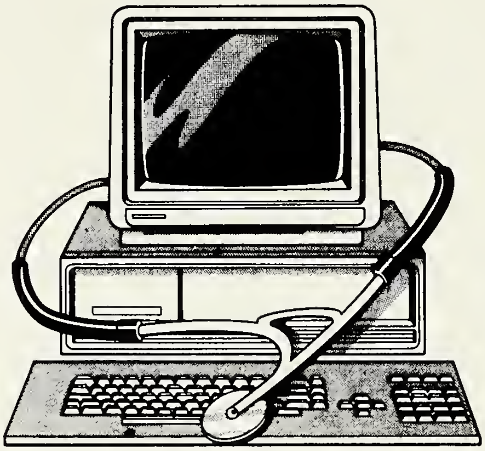

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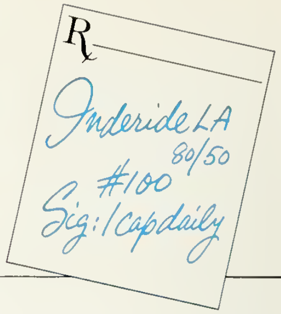

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Propranolol hydrochloride (INDERAL® LA)	80 mg
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No 459—Each INDERIDE® LA 160/50 Capsule contains	
Propranolol hydrochloride (INDERAL® LA)	160 mg
Hydrochlorothiazide	50 mg

INDERIDE LA is indicated in the management of hypertension

This fixed-combination drug is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, therapy with the fixed combination may be more convenient than with the separate components.

CONTRAINDICATIONS
Propranolol hydrochloride (INDERAL®):
Propranolol is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol

Hydrochlorothiazide:
Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs

WARNINGS
Propranolol hydrochloride (INDERAL®):
CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated, and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics and the response observed closely, or propranolol should be discontinued (gradually if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced and the patient carefully monitored In addition when propranolol is prescribed for angina pectoris, the patients should be cautioned against interruption or cessation of therapy without the physician's advice If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure

Hydrochlorothiazide:
Thiazides should be used with caution in severe renal disease In patients with renal disease, thiazides may precipitate azotemia In patients with impaired renal function, cumulative effects of the drug may develop

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma

Thiazides may add to or potentiate the action of other antihypertensive drugs Potentiation occurs with ganglionic or peripheral adrenergic-blocking drugs

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported

PRECAUTIONS
Propranolol hydrochloride (INDERAL®):
GENERAL Propranolol should be used with caution in patients with impaired hepatic or renal function Propranolol is not indicated for the treatment of hypertensive emergencies

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that propranolol may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

CLINICAL LABORATORY TESTS Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs, such as reserpine, should be closely observed if propranolol is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

PREGNANCY Pregnancy Category C Propranolol has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximal recommended human dose There are no adequate and well-controlled studies in pregnant women Propranolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

NURSING MOTHERS Propranolol is excreted in human milk Caution should be exercised when propranolol is administered to a nursing mother

PEDIATRIC USE Safety and effectiveness in children have not been established

Hydrochlorothiazide:
GENERAL Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely Hyponatremia hypochloremic alkalosis, and hypokalemia Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids Medication such as digitalis may also influence serum electrolytes Warning signs irrespective of cause are: Dryness of mouth, thirst, weakness lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria tachycardia, and gastrointestinal disturbances such as nausea and vomiting

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH

Interference with adequate oral electrolyte intake will also contribute to hypokalemia Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effect of digitalis (eg, increased ventricular irritability) Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content

Any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather, appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening In actual salt depletion, appropriate replacement is the therapy of choice

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy

Insulin requirements in diabetic patients may be increased, decreased, or unchanged Diabetes mellitus which has been latent may become manifest during thiazide administration

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy

Thiazides may decrease serum PBI levels without signs of thyroid disturbance

Calcium excretion is decreased by thiazides Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy The common complications of hyperparathyroidism, such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function

DRUG INTERACTIONS Thiazide drugs may increase the responsiveness to tubocurarine

The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient Thiazides may decrease arterial responsiveness to norepinephrine This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use

PREGNANCY Pregnancy Category C Thiazides cross the placental barrier and appear in cord blood The use of thiazides in pregnancy requires that the anticipated benefit be weighed against possible hazards to the fetus These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult

NURSING MOTHERS Thiazides appear in human milk If use of the drug is deemed essential, the patient should stop nursing

PEDIATRIC USE Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Propranolol hydrochloride (INDERAL®):
Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular Bradycardia congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System Lightheadedness, mental depression manifested by insomnia, lassitude weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal Nausea, vomiting, epigastric distress, abdominal cramping diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory Bronchospasm

Hematologic Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

Hydrochlorothiazide:
Gastrointestinal Anorexia, gastric irritation, nausea vomiting, cramping, diarrhea, constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis, sialadenitis

Central Nervous System Dizziness, vertigo, paresthesias, headache; xanthopsia

Hematologic Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia

Cardiovascular Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics)

Hypersensitivity Purpura, photosensitivity, rash; urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress, including pneumonitis, anaphylactic reactions

Other Hyperglycemia; glycosuria, hyperuricemia, muscle spasm; weakness, restlessness, transient blurred vision

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn

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MODERN MEDICINE

Coverage

Daniel L. Dolan, M.D.

PERSONAL time-off is necessary for physician health and well-being in hectic modern practice. It necessitates coverage. Coverage requires the erection of systems within groups or individual practices, which are activated most commonly on weekends or holiday periods. The disadvantage is that serious medical problems presenting at these times are often, of necessity, dealt with by strangers unfamiliar with the patient. In the following true case report, each physician acted properly and effectively within the agreed upon rules of cross-coverage. The outcome would have been the same. This case report is presented to demonstrate the unwieldiness, re-traced steps, and fractionation of care that can result when acute illness encounters "the system."

Mr. A., a 79-year-old gentleman, went to the office of his physician, Dr. 1., on a Friday morning because of low back pain. Dr. 1. was out of town and his patients were being transferred to Dr. 2. who promptly saw him. The patient told of low back pain for several weeks and indicated that Dr. 1. had removed a carcinoma from his sigmoid colon in the spring of 1979 at a local hospital, and although he had undergone treatment, a recent check had revealed no evidence of recurrence. Dr. 2., a general surgeon, telephoned Dr. 3., an orthopedist, and arranged referral. Dr. 3. arranged for Mr. A. to be hospitalized following the telephone call and, this accomplished during the middle part of Friday, Mr. A. arrived on the ward at approximately 2 p.m. Dr. 3. arranged to have Dr. 4. see Mr. A. on evening rounds and assess his low back pain, since Dr. 4. was covering for his group that evening.

Dr. 4. arrived on the ward at approximately 6 p.m., but fifteen minutes earlier Mr. A. began having copious hemoptysis with blood pressure dropping to approximately 90 systolic. He was quite dyspneic and displayed bilateral rales when Dr. 4. examined him. Dr. 4. ordered an electrocardiogram and requested an internal medicine consultation urgently through the emergency room consultation card system, wherein an internist on the hospital staff would take all such calls for 24-hour periods in rotation. Dr. 5., up for the day on this list, had signed out to his partner, Dr. 6., who was contacted by telephone in his stead. Dr. 6. was unaware of this change, however, and having attained senior staff status wherein it was not necessary for him to take emergency room call, contacted Dr. 7., attending on the house staff teaching service, and arranged referral. Dr. 8., a senior house officer, and Dr. 9., his intern, saw the patient immediately with Dr. 7., the attending, and evaluated the patient over the next three hours. The patient's PaO_2 was 41.6 torr rising to 132.7 following 60% oxygen therapy. $PaCO_2$ was 36, the electrocardiogram revealed a right bundle branch block with right axis deviation and sinus tachycardia, and the chest x-ray showed interstitial markings bilaterally, fluid at the right base, cardiomegaly, and a possible right hilar mass. A platelet count was 35,000; prothrombin time was 17 seconds with a control of 12.6. Partial thromboplastin time was 39.8 seconds with a control of 32.9. Because of the massive episodic hemoptysis, neoplasm was considered more likely than pulmonary embolus or congestive heart failure. A pulmonology consult, Dr. 10., was obtained rapidly to consider bronchoscopy. Dr. 10. raised the possibility of bronchiectasis. The patient had stopped hemorrhaging by this time, and it was felt best to more fully evaluate his clinical and hematologic status the following morning before bronchoscopy.

On Saturday morning an SMA was obtained, showing an alkaline phosphatase greater than 350, an LDH greater than 600, an SGOT of 160, and a glucose of 234 (I.V. running). A sputum culture and Gram stain revealed normal flora. A diagnosis of disseminated intravascular coagulation was felt likely. Dr. 11. replaced Dr. 8., being on-call for that day, and Dr. 12. replaced Dr. 10. as pulmonology consultant, also covering for the weekend. Dr. 11., learning of the patient's earlier sigmoid carcinoma in a different hospital, telephoned the medical record department there, where the chart was pulled and the discharge summary read to him. At this time it was discovered there had been a second admission two years after the first, wherein a routine follow-up barium enema revealed a number of filling defects. He was hospitalized at that time under a gastroenterologist, Dr. 13. who had biopsied the areas and found villous adenomas. A right infra-hilar mass was found on chest x-ray, however, and bronchoscopy by Dr. 13a., a pulmonologist, had revealed a grade 2 adenocarcinoma, which was considered microscopically identical to the sigmoid carcinoma removed two years previously. Dr. 11. now contacted Dr. 13. by telephone confirming these data and learning that oral 5-fluorouracil had subsequently been administered by Dr. 1. with subsequent shrinkage of the lung mass.

Mr. A. remained stable on Saturday. Dr. 12. felt that bronchoscopy would be hazardous with the abnormal coagulation studies and all agreed that the lesion was now most likely a recurrence of the metastatic adenocarcinoma in the right hilum. On Sunday, Dr. 14. (medical oncologist) saw the patient in consultation, suggesting fresh frozen plasma and platelet transfusions if bronchoscopy was to be pursued. Bronchoscopy was disadvised at this time, however. Discussions were held with the patient and family

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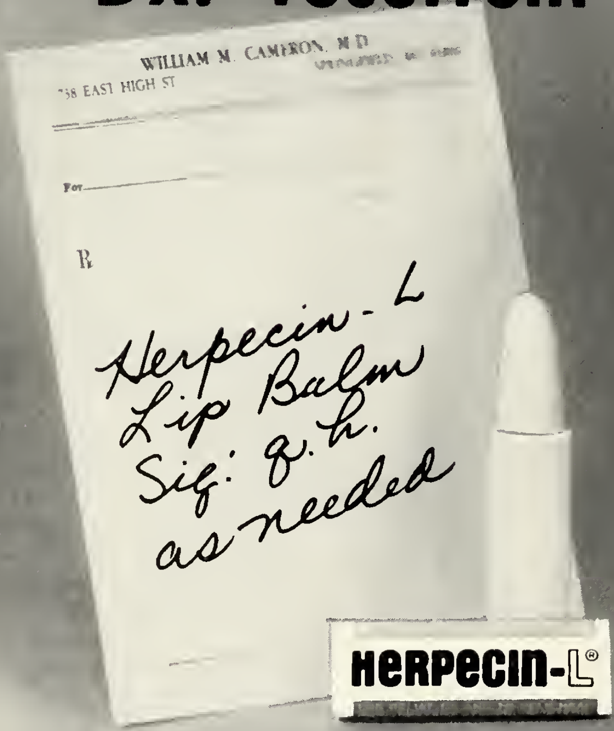
From Mountain AHEC, 501 Biltmore Avenue, Asheville 28801

by Dr. 7. and it was mutually decided and supported that ''do not resuscitate'' orders be instituted. This was accomplished although caradiac arrest was not anticipated. Unexpectedly at 4:30 a.m. on Monday, the patient experienced a cardiac arrest and expired. Postmortem examination was not obtained.

Fourteen physicians were directly or indirectly involved in this patient's 72 hour acute illness.

Dx: recurrent herpes labialis



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Ethical Quandaries for the Present Day Medical Institution

Eben Alexander, M.D.

- *Physicians seeking to do no harm in today's complex medical institution need special leadership to guide them through the ethical mazes that confront them.*

IT IS no great revelation that life is becoming more complex and more expensive. It costs more to heal people, to kill people in warfare, to educate people, and to feed people. All of these increasingly complex areas have created special problems and ethical considerations, but probably none more so than our own area — the care of the sick and the preservation of health.

It was not until about 1913 that a patient could visit a physician and have a better than fifty-fifty chance of being improved thereby. Since then, the tools, the drugs, the diagnostic methods, and the uniformity of medical training have improved so greatly that it is a rare patient who cannot expect some relief from such a visit. However, that patient can also be hurt by ill-advised treatment, and therein lies some of the problem.

I read in the *Chicago Tribune* recently that the horseless carriage had just about gotten rid of chivalry (and virginity); that nuclear arms had just about gotten rid of war; and that air conditioning was about to ruin the Old South. Of course the writer was referring to the fact that air conditioning has made the climate bearable enough that people are moving south in increasing numbers and bringing with them ethnic and regional characteristics that dilute and change the character of our area. Whether those changes are ruinous or not is debatable, and is not relevant here. I use the story to illustrate how technological advances force change on a society. In the field of medicine the rapid advances in technology that have changed the character of medicine have brought with them inordinately complex ethical considerations.

I have been told that the philosophical study of ethics in our higher educational institutions had hit a "slough of despond" until medical ethics came along to enliven it — and certainly it has been enlivened.

I know some of what the ethicists say about the complex issues imposed on medicine by modern technology, and it is obvious that they view with disdain the "unsophisticated" physician struggling with ethical decisions on a day-to-day basis. That disdain leads them to discuss ethics in philosophical terms difficult to understand. Their language is about as understandable to us as that we use is to the patient who is told that he is going to have "a craniotomy for a cerebellar spongioblastoma" — or "receive 3025 rets of Cobalt-60 through a lateral portal." When we physicians clothe our expertise in the complexity of our language, we do not help our patients to understand their condition, just as the ethicists do not help us with day-to-day decisions unless they can state the problems in day-to-day language. Until that time comes, we have to stumble along on our own.

Medical care was simpler before the tremendous advances in technology and therapeutic drugs took place, advances that enable us to prolong life under circumstances that may or may not be of value to the patient. When and how to use these advances become increasingly difficult decisions to make as more of them become available, and it becomes increasingly difficult to remember the injunction that should always be applied in medical practice — "First of all, to do no harm."

We can all feel comfortable with that particular injunction, but how best to adhere to it is not always clear. I have found two guides to be very useful: 1) the patient's rights must always be respected; and 2) when values differ, the patient usually should be taken care of according to his, not the physician's, values. Social and economic factors affect all of these ethical decisions, but if they become the most weighty factors they will surely distort our ethical approach to medical care.

The physician must constantly be aware that he serves as the patient's advocate. No one else is trained to do it as well; no one else has a professional tradition in that role; no one else believes himself or herself as willing to do it. As patient advocate, however, the physician will invariably sometimes find himself at odds with the institution of which he is a part.

Institutional ethical quandaries in the care of the patient are of such quantity that we can only touch on a few of them. Warshauer recently discussed one aspect of the problem when he addressed the possible conflicts between medical and religious institutions.[1] He applied the term "medical institution" to the philosophy of the practice of medicine; throughout this paper I use the term in the sense of a medical center or hospital complex. Institutions that provide medical care are as necessary to our continued

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From the Section on Neurosurgery, Department of Surgery, Wake Forest University Medical Center, Bowman Gray School of Medicine, Winston-Salem 27103.

existence as a civilization as are our schools, our police departments, and our fire departments. The problem is how to help medical institutions keep the proper perspective. The word ''institution,'' in the sense of a facility and those who run it, unfortunately implies a cold, unfeeling organization seeking primarily its own welfare and survival. Since the physician has been affiliated with a medical institution from medical school onward and is an essential part of a medical institution, he or she is probably better able to judge what that institution can and should do on behalf of the patients, and those things that it should not do. This ''inside'' knowledge demands that physicians be ''as wise as serpents and harmless as doves'' (Matthew 10:16).

Nothing in what I have just said should be taken to imply that all those who run organizations providing patient care are unfeeling persons or are unappreciative of the needs of the patients. However, by the nature of their positions, their interests are primarily in the stability, the future, and, in some instances, the very survival of their institutions.

The cost of modern medical technology is so great that certain procedures can only be done if an institution elects to support their use. One institution may transplant baboon hearts into certain babies with congenital heart problems. Another institution may decide to invest the millions of dollars necessary to implant mechanical hearts in certain adults with heart disease. Still another institution may decide that heart transplantation is not sufficiently advanced for the institution to participate in it and, even though the institution's staff may have the highest technical ability of any institution in the country, it may choose to take another direction.

These examples of experimental problems have profound ethical connotations for a committee of trustees, for a committee of medical staff, and for an ethics committee. Let us look at some more practical examples.

Despite the relatively generous federal support for the 70,000+ people in the United States now on renal dialysis, some institutions may decide to forego dialysis for end-stage renal disease. As a consequence, those institutions may have to agree not to participate in renal transplantation either, despite the fact the renal transplantation, while not without problems, has given victims of end-stage renal disease a gratifying quality and prolongation of life.

Or, an institution may elect not to have an intensive care nursery to take care of premature babies or newborn babies with congenital anomalies. The level of expertise now available to these children complicates that decision. If in 1960 the decision had not been made to resuscitate any neonate weighing under 1000 grams, the expertise that has been developed since would be no further along now than it was then. However, with that expertise, the 1000-gram neonate now has a good chance of survival and a normal life expectancy.

It is necessary sometimes to invest in some of the advances of medicine simply because of the increasingly impressive experience that has been gained. The reduction of mortality after coronary artery bypass operations from 18% to 1.5%, and to even less in selected groups of patients, is a very marked improvement. The testimony of numerous patients who have been relieved of unstable angina by the procedure and who feel that they have had their lives prolonged provides increasing vocal support for the procedure.

Plasmapheresis is a complex procedure that is being used for diseases thought to have immunologic connotations, such as myasthenia gravis and multiple sclerosis. It is new, and it is expensive. However, it, and other such new and experimental procedures, should continue to be used if they appear to be effective. They will continue to be expensive, and will continue to be supported only if physicians intelligently and articulately justify their use, whether at the experimental stage or only after their therapeutic benefit has been proved.

No longer can a single institution offer all services to all people. When should expensive, complex, experimental machines and procedures be covered by the institution's own funds? How does the physician maintain his traditional role as patient advocate when the institution faces the difficult choices of what patients to admit, what services to offer, and what research to follow?

No institution can expect to anticipate all the needs of the future or expect always to make the right decisions. Reliance must therefore be placed on the expertise, the vision, and the understanding of physicians within the institution. The danger of not being able to continue to improve patient care is great, and will be prevented only by the continued efforts of all involved. The ethical quandaries of medical progress dictate that physicians, while remaining patient advocates, involve themselves also in institutional politics, management and financial problems, and the equitable delivery of medical care.

I was privileged to be a professor of neurosurgery in a church-related institution with a strong religious base, a strong pastoral care program, and ministers of all faiths who were interested in cooperating with the institution and its physicians to assure the optimal care of patients. Over my 20 years as the Chief of Professional Services I learned some valuable concepts. I did not learn the ultimate answer to the ethical quandaries facing medical institutions, but I learned the following relevant facts:

I learned that an institution is only as good as the people who run it, and therefore it is important to assure that the right people are in charge.

I learned that a good name and a good reputation alone are not sufficient to keep even the best institution on the right track.

I learned that good working relationships need to be achieved at all levels by physicians working in institutions and only in that way can the physicians be of value in solving ethical questions and be assured of having the tools with which to work for the future.

In conclusion, I learned that the best patient care is provided and many of the ethical quandaries are diminished whenever compassion, understanding, technical skill, the best possible tools, recognition of patient and family roles, the best ancillary services, and the best trained physicians and administrators are combined in a balanced potpourri of what we know as a medical institution.

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On the Importance of Small Things

Douglas S. Diekema, M.D.

- *This is an address delivered by Dr. Diekema, Co-President of the class of 1985, at Commencement Exercises at the University of North Carolina School of Medicine, May 12, 1985.*

ON this, the day of our medical school commencement, we find ourselves entering a profession which has been engulfed by the big things of this world . . . big technology, big business, big finance, big research, big politics. The era of the small town solo practitioner, we're told, is over. We now live in the age of the medical-industrial complex, the health maintenance organization and the CT scanner. We enter medicine during a period of uncertainty — uncertainty as to which direction it will go and where it will end up. Seemingly, we are on a sharp turn, unable to discern what lies ahead.

Three years ago the Merrimon lecturer Arnold Relman, editor of the *New England Journal of Medicine*, predicted: "If we cling to our present course, I am convinced that the independence and ethical base of our profession will be progressively eroded and the practice of medicine will continue to evolve into commerce."[1] Lewis Thomas has had similar thoughts. Says he: "If I were a medical student or intern, just getting ready to begin, I would be apprehensive that my real job, caring for sick people, might soon be taken away, leaving me with the quite different occupation of looking after machines."[2]

We, as the future practitioners of medicine, can no longer ignore these forces. We must respond to the challenge of shaping the course of medicine. And in this age of big things, I would like to propose a starting place. I would like to make a plea for the importance of small things. In an age where one gains recognition by developing artificial hearts or implanting a baboon heart into a dying baby, I want to propose that we proceed into the profession of medicine bearing a new set of values. I propose that we debunk those that rule medicine today — the values that state that only the big things are worthy of recognition; that measure success in terms of money, power and recognition; that give precedence to technology over human warmth.

Our real influence in patient care comes through the small things. No CT scanner will ever be as powerful as abdominal palpation in its ability to soothe the patient. For the human touch implies caring. The lingering of the physician's fingers on the patient's wrist after taking the pulse carries a message of concern and support. No drug can ever replace that human concern.

I would contend that the real heroes of medicine are not the William DeVrieses of the world. They get their rewards in recognition and financial gain. The true heroes are those who give of themselves — give of their joy, their interest, their understanding, their humor, their time, their concern. It is the harried pediatric resident who has yet to do three new patient work-ups, two IVs, and one Gram's stain who takes a few moments anyway to stop and play with a frightened six-year-old — an act that will never be reported in any newspaper, but the effect of which will live forever in that child. It's also the busy family doctor who spends an extra thirty minutes in the nursing home holding the hand of his eighty-seven-year-old patient, sharing her struggle with the ever-present reality of death.

Indeed, the true greatness of our profession is not to be found in newsworthy medical breakthroughs, but rather in these small everyday acts — the warm caring touch, the look of concern, the calming word, and the listening ear.

As individuals we need not change everything we see that is wrong. We need only find our small place in the scheme of things and then do something in behalf of a better world. We don't need to change all of medicine, just those small things we encounter daily which might help make someone's day a bit brighter. In her moving book, *A Parting Gift*, Dr. Frances Sharkey describes her last days with a dying eight-year-old leukemic patient: "I couldn't save him, and I couldn't tell him what death was like. But I could rub his back. . . . There is no such thing as a perfect moment. We make all our moments, and by the truth and love we bring to them, we make them perfect."[3]

Our technology may fail, our medicine may cease to heal and our laboratory tests may tell us the diagnosis is terminal. At that point, only love remains: our ability to act compassionately, ease the pain, decrease the loneliness. As long as we are willing, the human element we bring to medicine will remain our most potent therapeutic agent.

The poems of Emily Dickinson contain much wisdom. She too recognized the importance of serving in small ways when she wrote:

> If I can stop one heart from breaking,
> I shall not live in vain:
> If I can ease one life the aching,
> Or cool one pain,
> Or help one fainting robin
> Unto his nest again,
> I shall not live in vain.[4]

This commencement indeed represents a big step for all

From 234 McCauley Street, Chapel Hill 27514.

of us. But finally, even as we savor this moment, let's not forget the importance of the other small things in our lives — those people and things which are prone to be neglected at the expense of our "higher" goals. So relish the moment of becoming an M.D. for a while. But when you go home tonight, after you've tucked the kids into bed and kissed them goodnight, go back outside. Stop on the porch and breathe the fresh night air. Savor the fragrance of roses in the yard. Spend some time watching the squirrels as they play their balancing games in the branches above you. Call for the dog and watch him bound up with wagging tail and dancing tongue. Think about the richness these small things have added to your life. Wander back inside. Read some poetry. Tell your spouse you love him or her. Better yet, show your love by doing the dishes. Take some time to laugh together.

The small things in life. Let us never forget them, lest we forget life itself. My wish for all of us is that we may find joy in those things that do not make the news.

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George M. Cooper, Jr., M.D. (1919-1984)

In the life of a young man the most essential thing for happiness is the gift of friendship.

Henry Cushing, *Life of Sir William Osler*

. . . It's a lot more than who he was; it's what he was. George Cooper, that is.

Sure, he was a physician, and was ranked with the best, both as a clinician and as a consultant. But he was also someone's son, someone's brother, a very special someone's husband, and one very fortunate young man's father. He was a civic and community-minded churchman, a man of God. He was a friend to many.

He was my friend; he was as close to me at times as breathing. Our senses of humor were nearly always synchronized. "The pun is the lowest form of humor," some say, but he loved 'em. When George cleared his throat to tell a story, and cleared a couple more times in the telling of it, you could be sure it would be good. Not always printable, as A.C. and Al will attest, but always entertaining.

Coop loved to play cribbage, and was skillful as well as lucky. He was good at cards; the only one I've met better than I, but he definitely was. We played together for over twenty years. Considering the many gaps his absence has created for so many, this will seem trivial to most. Nevertheless, he will be missed by some when the cards are shuffled and dealt and there is no hand for him.

He was part sandy beach, part cool mountain stream. He was all gentlemen, knowing what to do, how to do it, and when it was appropriate. He loved to win, but knew how to lose and maintain his poise. He "took turns winning" with his colleagues at work.

George was part camera, part film, and when he focused himself and his instrument, mountain streams gurgled and missiles roared heavenward from their pads.

He loved music, especially classical, but also natural. He recorded the crash of Atlantic waves on New England's shore as surely and as accurately as any tape recorder could.

. . . And on and on it could go, but by now the message is obvious. There will never be another like him, and we miss him. . . .

W. H. Bland, M.D.
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Cary 27511

DEMOGRAPHY

Distribution of Women and Minority Physicians in North Carolina

Mary Anne Salmon and Jane Stein

- *Women physicians are not, and minority physicians are, improving equity of access to medical care across North Carolina.*

NORTH CAROLINA physicians[1] are not distributed across the state in a manner comparable to the general population distribution. They are proportionately over-represented in the Piedmont and under-represented in the Coastal Plain while their numbers in the mountainous counties are approximately proportionate to the population. This distribution largely reflects the location choices of white, male physicians who constituted 85.8 percent of North Carolina's active, nonfederal physician population in 1982.[2] Does this same distribution apply to female and minority physicians or are their practices moving North Carolina closer to equitable access among the three regions of the state?

Data on the sex, race, and county of practice[3] for all licensed physicians, available from the Health Manpower statistics files of the University of North Carolina's Health Services Research Center, were used to construct figures 1-4. The racial category "Asian" in figures 3 and 4 includes physicians who reported themselves as "American Indian," "Oriental or Asian," "Spanish Origin" or "other" on their application for registration. Population data in figure 5 were taken from published data of the State Center for Health Statistics.[4] The assignment of counties to one of the three regions was made on the basis of a major terrain region map of the state,[5] and is shown in figure 6.

North Carolina's female physicians are more geographically concentrated than their male counterparts. Nearly three quarters of them practice in the Piedmont, and more than half of those in the Piedmont practice in the three Research Triangle counties — Durham, Orange and Wake. This concentration may be related to the different practice patterns of female physicians. Whether by choice or because of restricted opportunity, women physicians are somewhat less likely than men to be in solo, self-employed practice and much less likely to be in partnerships and group practices. Less than half of North Carolina's women physicians are in one of these practice types compared with over 72 percent of the male physicians.[6] The Research Triangle with its universities, medical schools and state

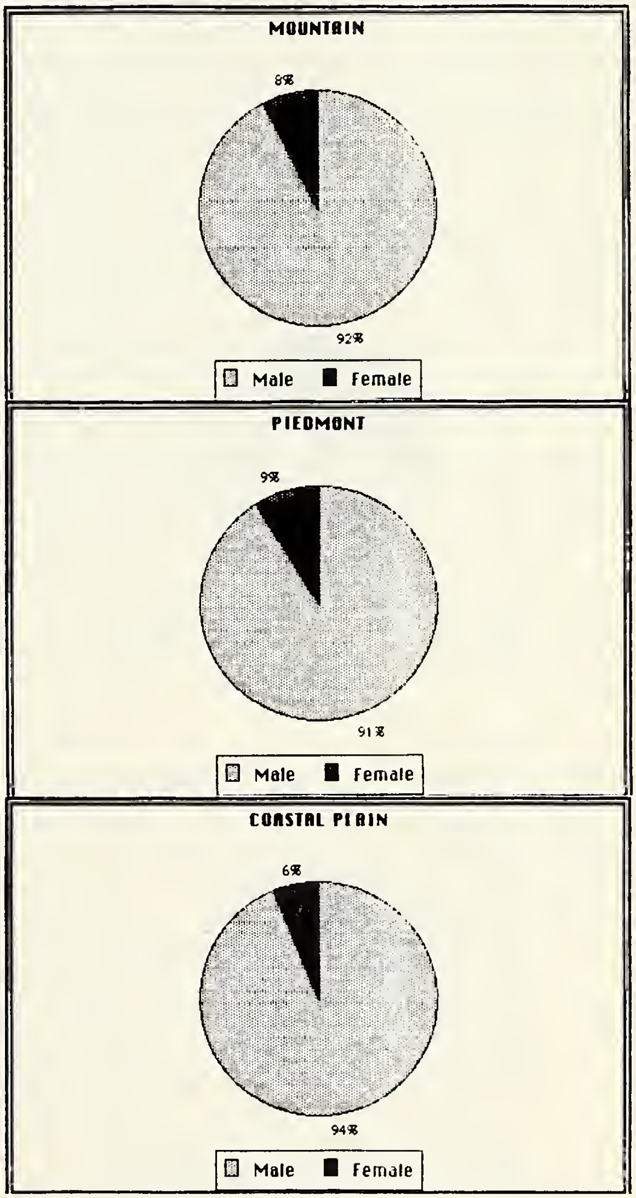

Figure 1. *Proportion of physicians, by gender, for the three regions of North Carolina, 1982.*

From the Health Services Research Center, Chase Hall 132-A, University of North Carolina, Chapel Hill 27514.

government provides opportunities in those areas outside of private practice where women physicians are more likely to be employed. Women doctors are only a little less likely than men to work in the mountains and in the major cities outside the Triangle but are considerably less likely to work in the Coastal Plain or in Piedmont counties that do not contain a city of 100,000 or more.[7]

While women doctors are more geographically concentrated than men, both black and Asian doctors are somewhat less concentrated in the Piedmont than white doctors. Still the majority practice in that region. Within the Piedmont the practice patterns of the two ethnic groups are quite different. Black physicians are over-represented in the counties that house the state's largest cities — Mecklenburg, Guilford and the Triangle — while more than half of Asian and other physicians practicing in the Piedmont are in the smaller, more rural counties.

Both black and Asian doctors are also more likely than whites to practice in the Coastal Plain where over a third of the population is not white and almost half of the state's non-white population lives. By contrast, they are very much under-represented in the mountains though the Asian doctors are more likely to practice there than are black doctors. It might be imagined that since the mountains are home to most of the state's American Indian population that American Indians would account for some of the "others" in practice in the mountains. However only one of the state's seven (all male) non-federal American Indian physicians is in practice there.[8] As in the remainder of the state, more than 90% of the "Asian" category of doctors in the mountains are, in fact, Asian.

From these data it can be seen that minority physicians are helping to reduce North Carolina's geographic inequity in access to physicians. However women physicians, 83.5 percent of whom are white, remain concentrated near the state's major medical centers.

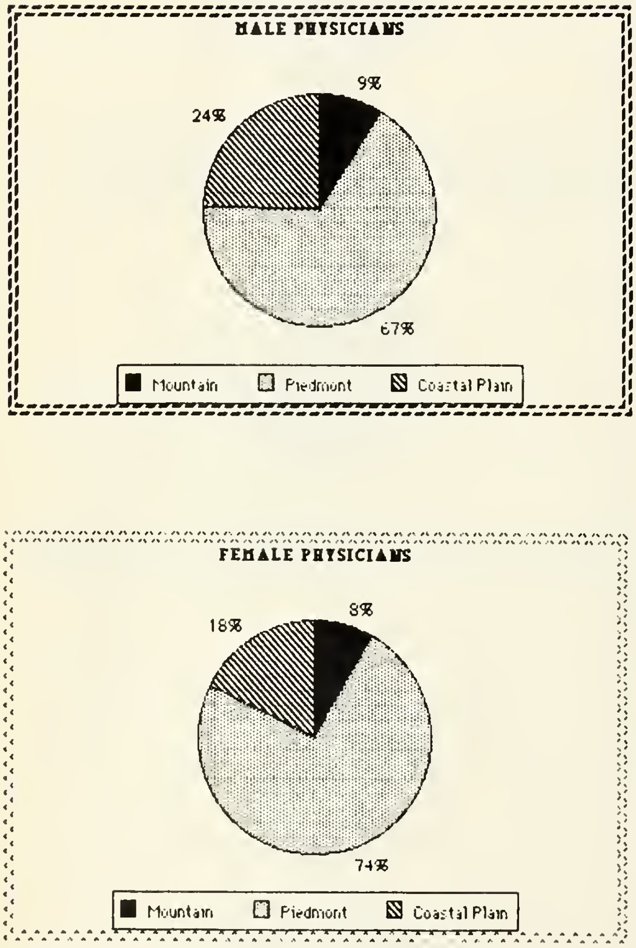

Figure 2. *Regional distribution of physicians for each gender, North Carolina, 1982.*

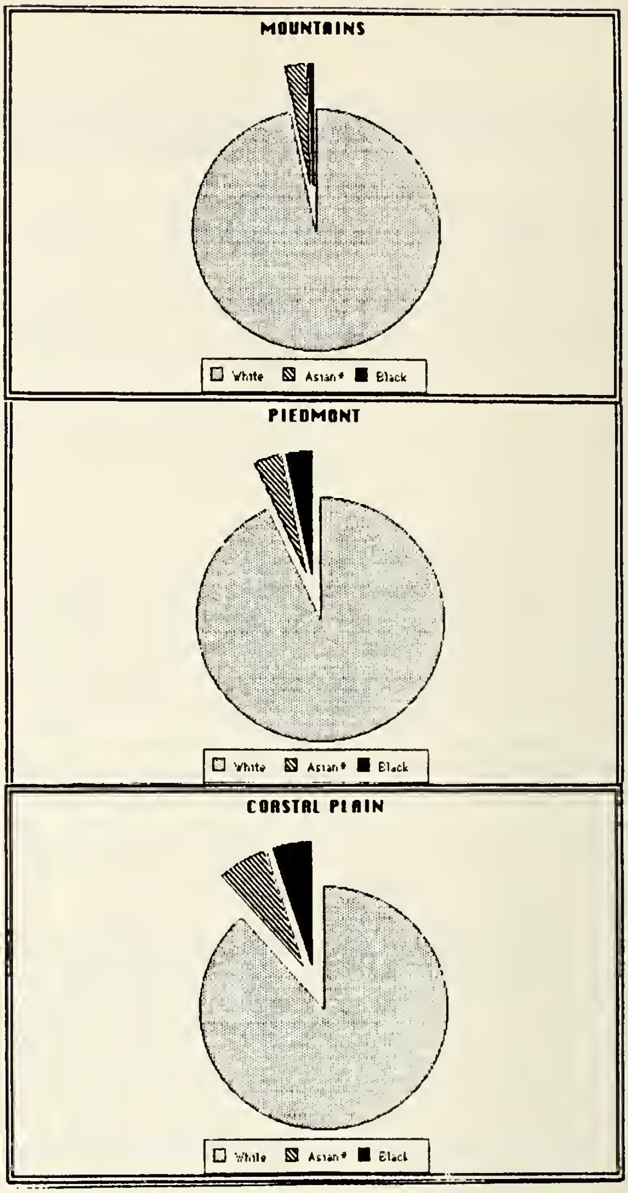

Figure 3. *Proportion of physicians, by race, for the three regions of North Carolina, 1982. The category Asian is over 90% Asian, but also includes American Indian, Spanish origin, and "other."*

Notes

1. This describes active, nonfederal physicians and does not include those currently

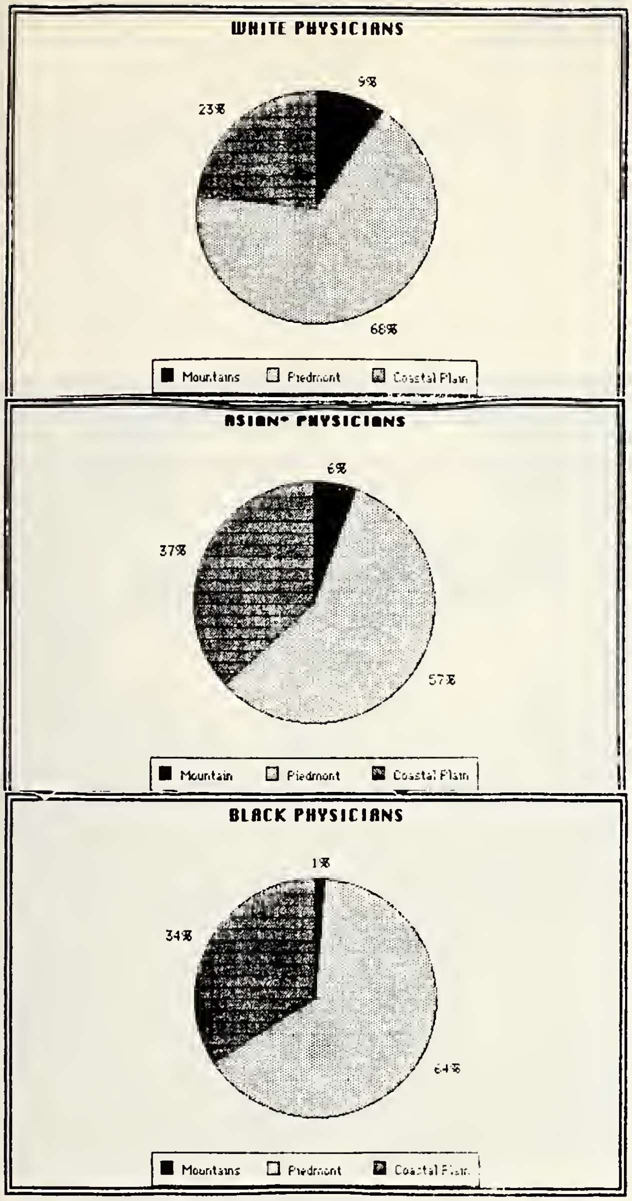

Figure 4. *Regional distribution of physicians for each race, North Carolina, 1982. The category Asian is over 90% Asian, but also includes American Indian, Spanish origin and "other."*

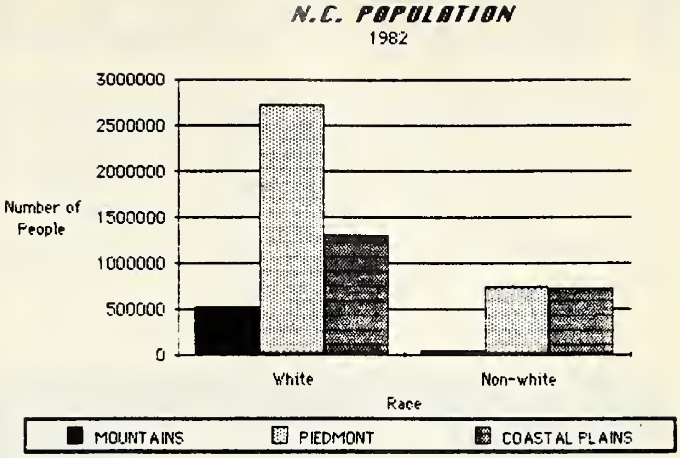

Figure 5. *Regional distribution of North Carolina's population, by race, 1982.*

participating in a post-graduate medical education program in North Carolina — i.e. residents.

2. Health Services Research Center. North Carolina Active Nonfederal Physicians, Specialties by State, County, HSA and AHEC, Effective: October 1982. Chapel Hill, North Carolina: Health Services Research Center, University of North Carolina at Chapel Hill, 1982.
3. Active physicians are assigned to county based on their business address. When business address is missing, home address is used.
4. State Center for Health Statistics. North Carolina Vital Statistics 1982. Volume 1: Births, Deaths, Population, Marriages, Divorce. Raleigh, North Carolina: Department of Human Resources, Division of Health Services. Office of Management Services, September 1983.
5. Lonsdale, R. E. et al. Atlas of North Carolina. Chapel Hill, The University of North Carolina Press, 1967, page 5.

   When a regional line passed through a county, that county was assigned to that region in which the greater part of the county lay. When a county was bisected by a regional line, it was assigned to the more eastern of the two regions.
6. North Carolina Health Manpower File. Health Services Research Center.
7. Cities of 100,000 or more are Charlotte, Durham, Greensboro, Raleigh and Winston-Salem. County and City Data Book, 1983.
8. Doctors on Indian Reservations are federal employees. Hence this paper understates the number of American Indian physicians practicing in the mountains of North Carolina.

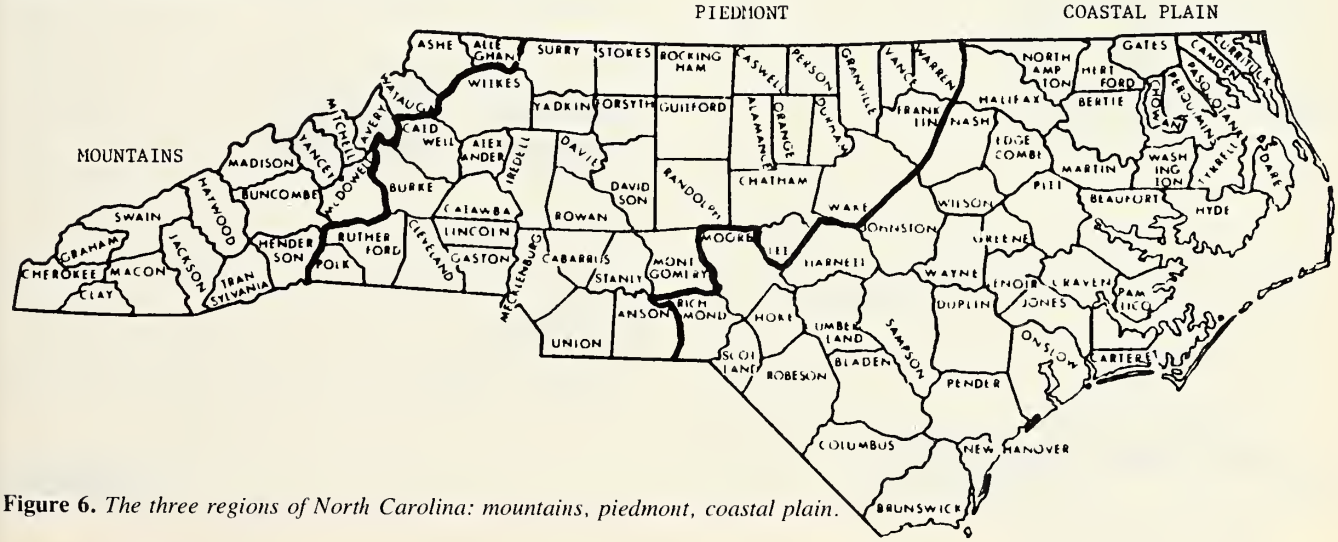

Figure 6. *The three regions of North Carolina: mountains, piedmont, coastal plain.*

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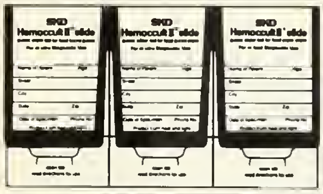

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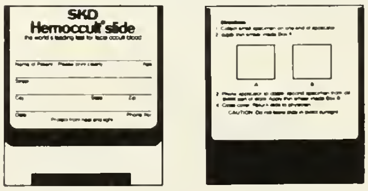

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President's Report to the North Carolina Medical Society

Linda P. Nance

I HAVE looked forward to this day, for I am excited to report to you that a tidal wave of action has rolled across North Carolina as auxilians have armed themselves to promote better health care, health education, health related legislation, and programs to combat social issues that undermine and destroy the health care which you work tirelessly to produce.

A successful child sexual abuse awareness program presented at the annual meeting was the necessary impetus for 30 county auxiliaries to present awareness programs for their members.

Armed with facts, auxilians have learned to discuss openly a subject we once pretended did not exist. Catawba county's leadership researched their community's needs and established a child abuse awareness program in their county's elementary schools with a goal to reach 8,000 students. Henderson, Cumberland, Gaston, Nash, Durham, and New Hanover-Pender counties offered outstanding awareness programs for their communities in coalition with many other agencies. Two of these counties offered week-long programs in which they promoted all aspects of child protection.

Through a grant from the Kate B. Reynolds Health Care Trust, video tapes of "Funny Tummy Feelings," a training program suitable for children in many settings which promotes awareness and prevention of child sexual abuse, was made available for training teaching volunteers. This program is available for any county auxiliary that wishes to use it. We hope this program will make children free from abuse, free to grow, free to develop, and free to become productive citizens.

Two smaller grants allowed us to print healthy living brochures and "Buckle Up" stickers. These have been distributed throughout the state to schools, at health fairs, and in physicians' offices. These carry the clear message that the North Carolina Medical Society Auxiliary wants to promote better health for its citizens.

At the direction of the Committee on Physicians' Health and Effectiveness, the auxiliary prepared, with the help of the medical society staff, a new *Helpline* brochure that better explains the purpose of this access line for physicians' families. This service, staffed by an auxilian, has been successful in offering aid to members of physicians' families in need of support for impairment.

Auxilians have helped to distribute the Medical Society's *Living Will*. It has been introduced at state meetings, through *Tarheel Tandem*, the "President's Newsletter," and during presidential visits to counties. It has been used in conjunction with organ donor awareness programs, and the Gaston County Auxiliary distributed copies to all of the nursing homes in their community.

More members than ever before attended the state meetings at which participants were offered programs about not only child abuse and neglect, but prenatal and postnatal care, automobile safety restraints, anorexia nervosa and bulimia, legislation, orderly financial planning, and parliamentary procedure.

Through the outstanding efforts of county leaders and members, exciting health projects are underway. County auxiliaries are working in coalition with forty-six other organizations to promote "Shape Up For Life" health projects in their communities. There are awareness programs designed to combat drunk driving, drug abuse, and child abuse. The Lenoir-Greene Auxiliary was instrumental in establishing a MADD chapter for the county, and auxiliaries are active in programs for cancer rehabilitation, foster parenting, organ donor awareness, cancer detection, and prenatal and postnatal care. In addition to these programs, auxiliaries promote CPR training, distribute "Shape Up For Life" pamphlets, contribute time and money to hospice, support and staff hands-on health museums, and produce health fairs. This year $81,000 was distributed to these projects through auxiliary efforts.

Mecklenburg County's endowment exceeded all expectations. It grew to $250,000 ten months ahead of schedule. An advisory board, composed of major Charlotte personalities was formed and MMAE's Inn, a Ronald McDonald type house, had its grand opening April 29. New Hanover-Pender County's similar goal is in its early stages, but is gaining active support among the citizens of that community.

North Carolina auxilians raised over $38,000 for the American Medical Association Education and Research Foundation through holiday sharing cards and other fundraisers. To help assure that medical education is not limited to the wealthy, counties contributed $3,800 to the state student loan fund. In addition, three percent of each member's dues was placed in this fund for North Carolinians enrolled in North Carolina's medical schools. Thirteen loans were made this year for a total of $18,500. Plans are under way to secure even larger sums of money for loans in

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From 1922 Brookhaven Road, Wilmington 28403.

the coming years.

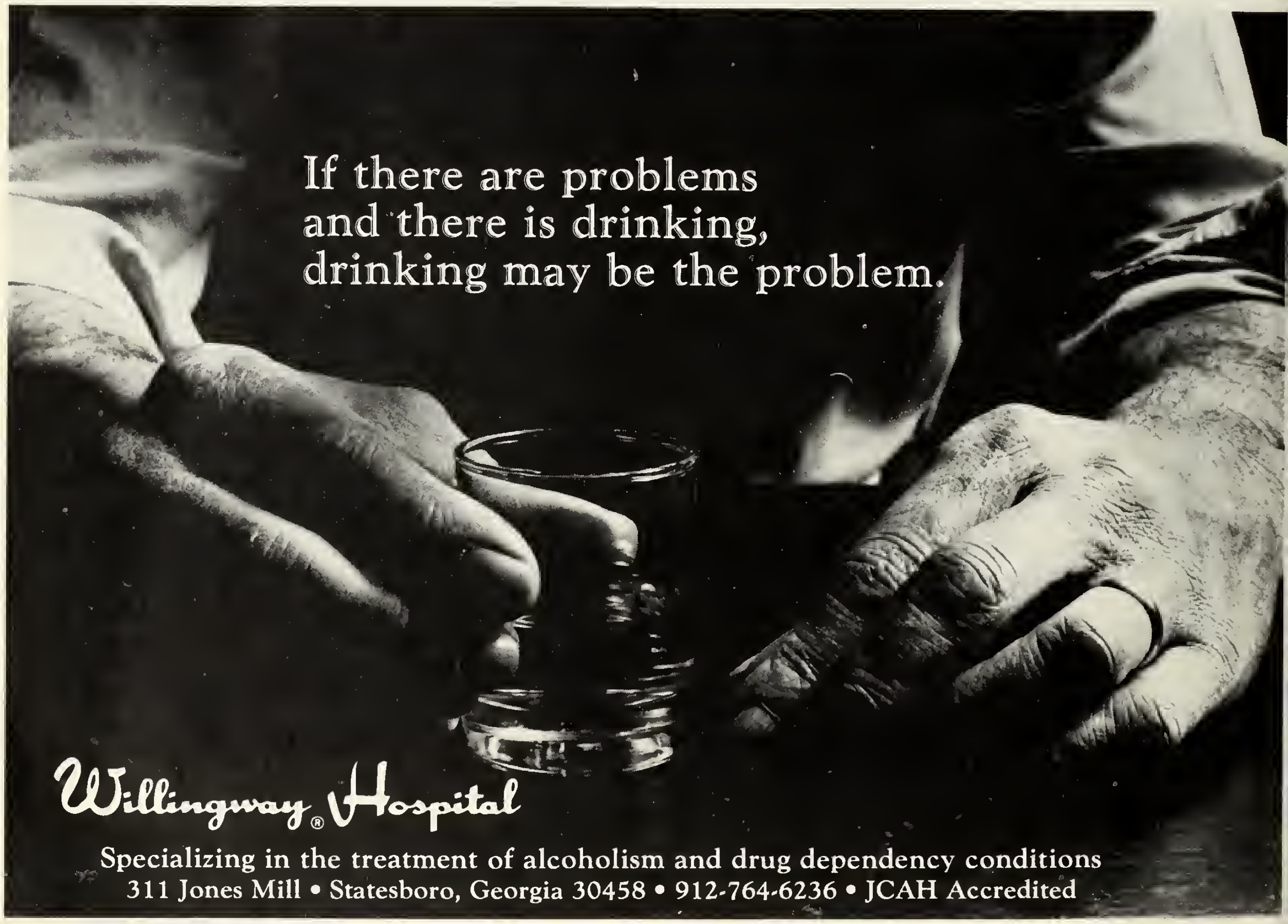
Besides the student loan fund, counties have awarded $24,000 to sixty students studying in allied health fields, and interest free loans to sixteen students have been made by several counties.

To assure that physicians will have a voice in the legislative process, counties have had outstanding participation in legislative programs and alerts. Twelve counties participated in the AMA's project *Medvote* in the fall of 1984. Auxiliary efforts made a difference in the voter turnout.

With so many outstanding projects and programs underway in the counties, the media has discovered this to be newsworthy. Buncombe, Cumberland, Guilford-High Point, Henderson, Nash and New Hanover-Pender counties thanked members of the media for their part in publicizing their many projects and programs with very successful media days.

Physicians' spouses across North Carolina have proven that more things happen when waters are stirred than when they are still. They accepted the challenge to make a difference in their communities. Our numbers grew as we worked to keep the federation strong. Make certain that your spouse is a member so we can push our membership toward the 100% mark of participation. The AMA's original constitution, now more than a century old, stated its objectives thusly, "to promote the science and art of medicine and the betterment of public health." Only our best efforts and our support will assure that every American will continue to receive the best health care.

The North Carolina Medical Society Auxiliary is proud to be your partner in this cause.



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President's Speech

Darlene Young

THIS year I am inviting you to SPREAD YOUR WINGS AND FLY! I hope that you will be open to new ideas, and ready to venture into new areas of concern. I believe that you can accomplish almost anything if you really believe in it.

Linda Nance and the sixty-one state presidents who preceded her have left a legacy of achievement of which we are all proud, but we cannot rest upon what has been done by our organization in the past. What matters now is what we hope to do in the future to build upon that foundation.

I believe that life is meant to be lived with joy, and that joy can be found through commitment and purpose. Dr. James T. Laney, President of Emory University, said in an address, "In each of your lives, there is the possibility of being drawn out of yourselves in those moments of ecstasy, of celebration, of participation in something that is noble and great and compelling, of service in a community in which your participation — by some alchemy that escapes our full comprehension — will give you not only a sense of reward but of joy."

I believe that we find purpose for our lives through service to others. This is a reward that our physician spouses have long enjoyed. To quote a familiar saying, "Service is the rent we pay for the space we occupy here on this Earth." Well, the auxiliary offers many opportunities for service. All we need is your interest and enthusiasm.

My major focus this year will be on day care for children. North Carolina has the largest percentage of working mothers in the nation. This is a serious problem for our state, and one of which we must be aware. Other areas of emphasis for the year will include: osteoporosis, teen alcohol abuse, day care for the elderly, problems of young adolescents, and malpractice support groups. Material on these subjects will be presented at the Fall Conference and the Mid-Winter Conference. We never drop viable programs from the past but each year we offer resource material in additional areas of concern so that the Auxiliary will always be in the forefront of current needs and trends. I hope that some part of the program material presented this year will inspire you to action.

The Auxiliary also offers excellent opportunities for leadership training. To paraphrase the television jingle, "Be all that you can be, you can do it in Auxiliary." Many who are active in Auxiliary go on to become leaders in community and state organizations. It's there if only you will take advantage of it.

Lately, there seems to be a pervasive negative feeling among many in the medical community. We often feel that the world is changing, and not necessarily for the better. We wish that life would just stand still for a while, but it won't. If things aren't going your way, you can just sit back and fuss and let life happen to you, or you can try to change things for the better. Individually or collectively, you can make a difference. You can work to improve health care in your community. You can act as a public relations advocate for your physician spouse. You can work diligently for legislation which will improve the quality of health care and the quality of life for all. Be a part of what we are trying to do. We need all of you and all of those who have not yet joined. Work hard on membership, not just local and state, but Federation membership, for there is increased clout in increased numbers.

As we start our work together this year, my prayer for you is found in a greeting written by Fra Giovanni in the thirteenth century.

> "I salute you! There is nothing I can give you which you have not;
> but there is much, that, while I cannot give, you can take.
> No heaven can come to us unless our hearts find rest in it today. Take Heaven.
> No peace lies in the future which is not hidden in this present instant. Take Peace.
> The gloom of the world is but a shadow; behind it, yet, within our reach is joy. Take Joy."

So, SPREAD YOUR WINGS AND FLY! Some of you may simply flutter from branch to branch, but at least you will have made a beginning. And, surely, some of you will soar like eagles, and that's a special blessing.

Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

October 16
Oxygen Use — CO_2 Narcosis and Ventilator Use
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

October 19-20
Jungian Techniques of Analytic Hypnotherapy
Place: Chapel Hill
Credit: 12 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

October 29
Crisis — Then & Now
Place: Kinston
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 800/662-7917

November 1-2
Alcohol and Drug Abuse
Place: Chapel Hill
Credit: 10 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

November 1-2
Review of the Management of SIDS and Near-Miss SIDS
Place: Chapel Hill
Credit: 7 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

November 14-15
Clinical Teaching and Evaluation of Clinical Performance
Place: Chapel Hill
Credit: 12 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

November 20
Endocrinology for the Lifetime of the Female
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

December 5-7
Fourth Comprehensive Symposium on Breast Disease
Place: Winston-Salem
Credit: 16 hours Category I AMA
Fee: $350.00
Info: Center for Medical Ultrasound, Bowman Gray, Winston-Salem 27103. 919/748-4505

December 5-7
Microcomputers in Medical Education
Place: Chapel Hill
Credit: 18 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

December 7
UNC Ophthalmology Resident's Day
Place: Chapel Hill
Info: Baird S. Grimson, M.D., 617 Clinical Sciences Building 229H, UNC, Chapel Hill 27514. 919/966-5296

December 12
Controversies in Transplantation
Place: Chapel Hill
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

December 18
New Uses of Calcium Channel Blockers
Place: Sanford
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage Street, Sanford 27330. 919/774-6518

OUT OF STATE

October 17-24
Review of Clinical Chemistry for Practicing Pathologists and Clinical Chemists
Place: San Diego, CA
Fee: $315
Credit: 40 hours Category I AMA
Info: Office of CME, ECU School of Medicine, Box 7224, Greenville 27835-7224. 919/758-5200, ext. 208

October 29-November 2
Diagnostic Imaging
Place: Southampton, Bermuda
Fee: $495
Credit: 25 hours Category I AMA
Info: Carl E. Ravin, M.D., Box 3808 DUMC, Durham 27710. 919/681-5268

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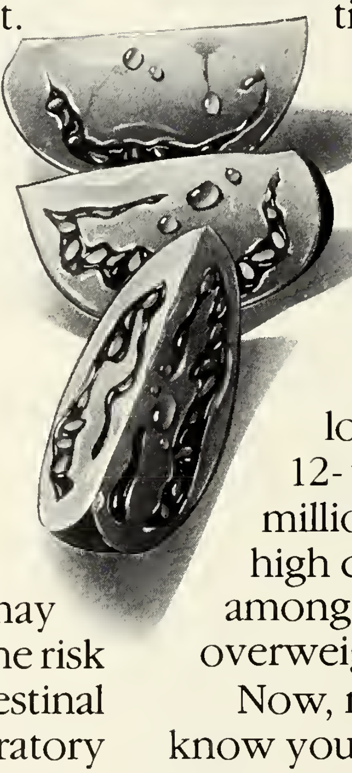
THIS SPACE CONTRIBUTED AS A PUBLIC SERVICE

A defense against cancer can be cooked up in your kitchen.

There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.

Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash and tomatoes, citrus fruits and brussels sprouts.

Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.



Fruits, vegetables, and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods like ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

Be moderate in consumption of alcohol also.

A good rule of thumb is cut down on fat and don't be fat. Weight reduction may lower cancer risk. Our 12-year study of nearly a million Americans uncovered high cancer risks particularly among people 40% or more overweight.

Now, more than ever, we know you can cook up your own defense against cancer. So eat healthy and be healthy.

No one faces cancer alone.

AMERICAN CANCER SOCIETY®

Studies in Process

UNC Investigators Study Drug for Treatment of Crohn's Disease

Drs. John Sessions and Eugene Bozymski of the Division of Digestive Diseases and Nutrition at the UNC School of Medicine are joining with clinical investigators at several other academic study centers in a clinical trial to evaluate Flagyl (metronidazole) as a therapeutic agent in patients with Crohn's disease (ileitis). The purpose of the study is to investigate the safety and efficacy of Flagyl as an alternative to prednisone and sulfasalazine. Recent trials have suggested that Flagyl is effective therapy for Crohn's disease.

Study participants will receive free medical care, a complete health evaluation, including determination of the extent and location of Crohn's disease, and study drugs for four months. Travel funds are available and parking will be paid. Patients who participated in the National Cooperative Crohn's Disease Study are eligible provided they meet the study criteria.

If you have a patient with moderately active Crohn's disease you would like to refer, we will be pleased to evaluate him/her for participation in the four-month study. During the study you will be kept informed of your patient's progress and upon completion of the study your patient will be returned to your care.

For further information, please contact either Dr. Sessions or Dr. Bozymski at 919/966-2511 or Alice Rupen, M.P.H., Crohn's Study Coordinator, at 919/966-5800.

Scans vs Angiograms in Pulmonary Embolism at Duke

The National Heart, Lung, and Blood Institute, through its Division of Lung Diseases, has initiated a multicenter study to determine the sensitivity and specificity of ventilation-perfusion scans compared with angiograms for the diagnosis of acute pulmonary embolism. The Duke University Medical Center, one of the six clinical centers participating in the study, is pleased to accept referrals.

The clinical diagnosis of pulmonary embolism is subject to a great number of false positives and false negatives. Pulmonary angiography, although considered diagnostic when coupled with an appropriate clinical history, is invasive, expensive and not without risk, and it requires special equipment and highly trained personnel.

The second method of diagnosis is a combination of perfusion and ventilation scanning. Current practice interprets a negative perfusion scan as solid evidence against the presence of an embolus, although there has not been a large-scale study to assess the sensitivity and specificity of the method. Long term patient follow-up that would determine clinical outcome of patients who had negative perfusion scans has not been carried out.

This study is designed to provide scientific basis for decision-making about patients suspected of having pulmonary embolism. It will assess the accuracy of ventilation-perfusion scans in predicting angiographic findings. These data should improve the diagnostic certainty and management of patients with thromboembolic disease and reduce morbidity, mortality and costs associated with the condition.

Patients 18 years of age or older with suspected acute pulmonary embolism are eligible for the study. Participants will receive a ventilation-perfusion scan and those with evident abnormalities will undergo angiography within 24 hours of the scan. Appropriate care will be initiated for patients diagnosed as having pulmonary embolism. Follow-up procedures depend upon diagnostic results. Patients who undergo angiography will be contacted by telephone at specific intervals after entry into the study to determine their status. Individuals who had normal perfusion-ventilation scans and those who had negative angiograms will be asked to return to the center for a complete history and physical examination three months after the first procedure. Subsequently these individuals will be contacted by telephone at regular intervals.

For more information on the study protocol or to refer a patient into the study contact Herbert A. Saltzman, M.D., or Lee Mallatratt, Clinical Coordinator, at 919/684-4149.

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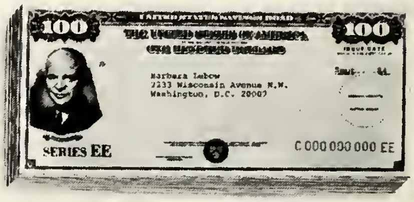
For more information, write to: Steven R. Mead, Executive Director, U.S. Savings Bonds Division, Department of the Treasury, Washington, DC 20226.



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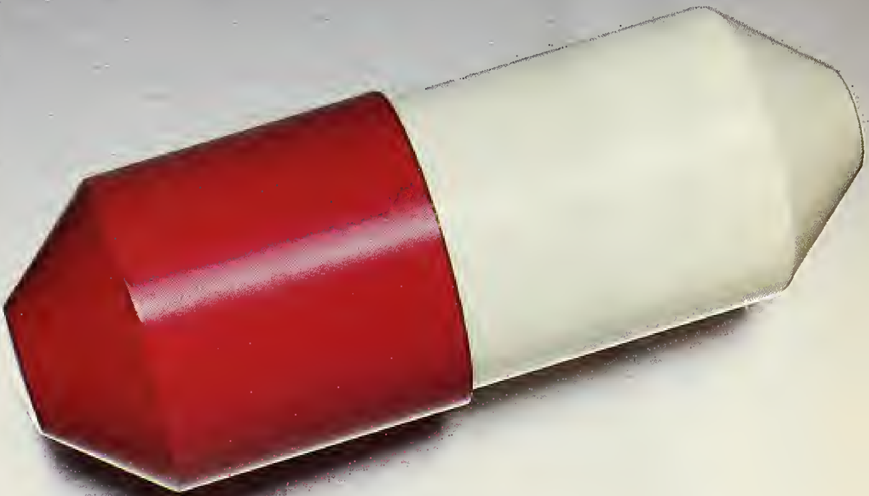
Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).



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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

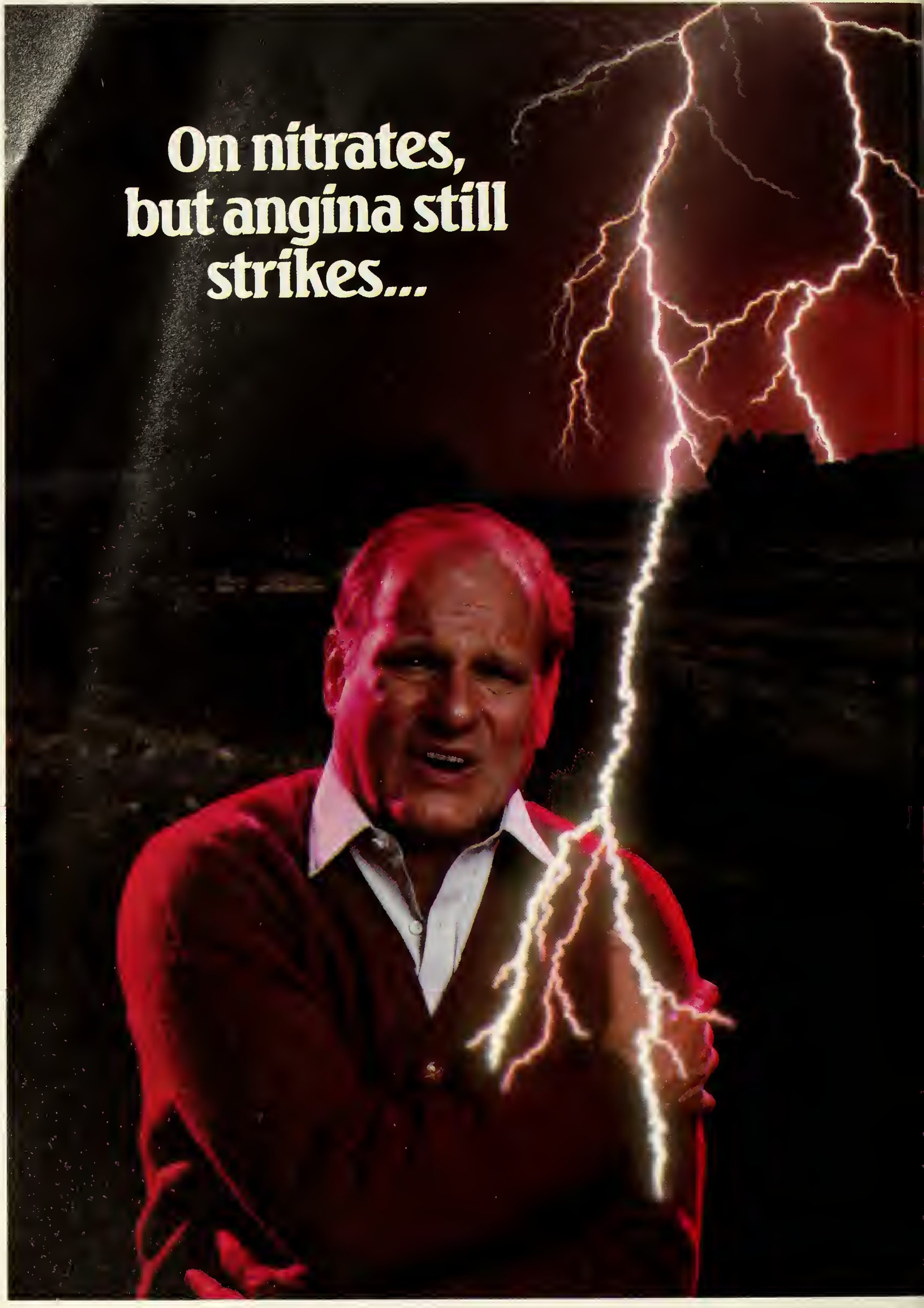
Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: **'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**
BRS-DZ:L39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With Isoptin, fatigue, bradycardia and mental depression are rare. Unlike beta blockers, Isoptin can safely be given to patients with asthma, COPD, diabetes or peripheral vascular disease. Serious adverse reactions with Isoptin are rare at recommended doses; the single most common side effect is constipation (6.3%).

Cardiovascular contraindications to the use of Isoptin are similar to those of beta blockers: severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no artificial pacemaker is present) and second- or third-degree AV block.

So, the next time a nitrate is not enough, add Isoptin…for more comprehensive antianginal protection without side effects which may cramp an active life style.

ISOPTIN. Added antianginal protection without beta-blocker side effects.

Please see brief summary on following page.

ISOPTIN®

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction < 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. (See *Precautions.*) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before ISOPTIN is used. (Note interactions with digoxin under *Precautions.*) ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild and controlled by decrease in ISOPTIN dose). Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment, however, four cases of hepatocellular injury by verapamil have been proven by rechallenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN. Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported. (See *Warnings.*) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shakiness, claudication, hair loss, macules, spotty menstruation. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984. 2385

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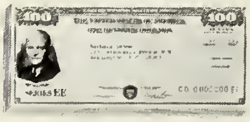

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Letters to the Editor

Joe Beard

To the Editor:

I was deeply moved by your tribute to Joe Beard (NCMJ 1985;46:303-9). He was a surgical resident at Vanderbilt when I entered medical school there, and while I was never privileged to know him personally, I admired him from afar.

The regular appearance and reading of the *North Carolina Medical Journal* helps this retiree feel he is not entirely out of the medical world and his favorite state. Your editorship is appreciated.

Alex X. Moffett, M.D.
70 W. Lucerne Circle
Orlando, FL 32801

Smokeless Tobacco: A Future Health Concern for North Carolina?

To the Editor:

Snuff dipping and tobacco chewing are habits that are rapidly gaining popularity in our country.[1] Moist snuff has increased domestic sales from 23.0 million pounds in 1978 to 37.1 million pounds in 1984 which is a 55% increase.[2] Sales for U.S. Tobacco more than quadrupled from 94.3 million dollars in 1973 to 443.7 million dollars in 1984. One publication claims there are 22 million users of smokeless tobacco in the United States.[3] Another indication of the increase in dipping and chewing is evidenced by the rise of "chewing clubs" spawned by this new tobacco craze in high schools and colleges, complete with charters, membership cards and even t-shirts emblazoned with mottos like "Don't spit on me."[3]

According to the tobacco industry, the "typical" tobacco dipper or chewer involves a wide range of adult men and may come from any section of the country; but the Southeast, Southwest and Midwest are the primary markets.[4] They claim that demand is greatest in the male 18 to 30 year-old group in these areas of the country. Currently, the tobacco industry is not actively promoting dipping and chewing for women.

Smokeless tobacco can produce significant detrimental effects on the soft and hard tissues of the mouth, including bad breath, discolored teeth, decreased ability to taste and smell, gum recession, advanced periodontal destruction of the soft and hard tissues, leukoedema and erythema of the soft tissue, leukoplakia, and for long-term users, cancers.[1, 5] Fortunately, the possibility of cancer at this time appears relatively low; however, a careful review of the North American medical and dental literature disclosed 646 documented cases of oral, pharyngeal, or laryngeal cancer which have been linked to smokeless tobacco.[6] Jayant et al suggested that the relative risk of developing oral cancer is 2.82 for smokers and 5.98 for chewers.[7] A case-control study of 255 women with oral and pharyngeal cancer and 503 women control subjects in North Carolina by Winn et al reported a fifty-fold increased risk of cancer of the gum and buccal mucosa in snuff-dipping, and relative risk of 4.2 percent for all mouth cancers in these women.[8] A 1985 prevalence study in Pitt County, North Carolina revealed approximately 15 percent of the adult population residing in the county use smokeless tobacco, which translates into approximately 14,550 users (unpublished observations).

Due to the time lag of use and manifestation of cancer, experts fear an epidemic of mouth cancer in 40 years. This fear is reflected in the latest of several demonstrations of concern:

- Rep. Tom Tauke (R-Iowa) introduced a bill that would tax smokeless tobacco.
- Rep. Mike Synar (D-Oklahoma) introduced a bill that would require warning labels on all smokeless tobacco and advertisements.
- Rep. Samuel Stratton (D-New York) introduced a bill that prohibits the advertising of smokeless tobacco (all tobacco) on any medium of electronic communication.
- Rep. Cardiss Collins (D-Illinois) introduced a bill that would set aside funds to educate youth regarding smokeless tobacco.
- On July 11, 1985, Massachusetts became the first state to require health warning labels on a smokeless tobacco product — moist snuff.
- Warning label bills are being considered in Delaware, Illinois, Michigan, New Jersey, New York, Oregon, Pennsylvania and Utah.
- In June, Surgeon General C. Everett Koop appointed a panel of scientists to review the health hazards of these products.
- Betty Ann Marsee of Ada, Oklahoma, charged in a $147.8 million suit against U.S. Tobacco Co. that her 19-year-old son Sean died in 1984 of tongue cancer from snuff use. The trial is scheduled for November 1985.

Considering the adverse health consequences associated with smokeless tobacco, the potential addictiveness of smokeless tobacco, the high prevalence of smokeless tobacco use in North Carolina and the potential health benefits accruing from smokeless tobacco cessation, or never initiating the habit, and based on my expertise in the area of smokeless tobacco I recommend and support that physicians in North Carolina consider the following:

1) the implementation of a warning label on smokeless tobacco containers;
2) the development of a smokeless tobacco cessation model for those currently addicted;
3) the support of health education in the public schools regarding the dangers associated with the use of smokeless tobacco — this education should begin early, when children are 7 and 8 years old; and
4) the enforcement of laws restricting minors from purchasing/selling smokeless tobacco products.

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Balloons on the CCU

To the Editor:

We would like your permission to reproduce in our new magazine, *MediScene*, your article entitled "Balloons on the CCU" by Charles Shunior, BSN, which appeared in April 1985 (NCMJ 1985;46:197-8).

This article would be reprinted in our pilot issue of *MediScene* which is a new magazine about medical care trends and is directed toward the public. We will be distributing the magazine to doctors for their offices.

Judy Marr, Editor
Michigan Medicine & Medigram
120 West Saginaw Street
East Lansing, MI 48823

Medical Mystery and the Whistle Blower: A letter to the author, Mebane Holloman Burgwyn

Dear Mebane,

Helen Dugan Allen, a classmate of yours, brought to my attention your article, "Medical Mystery and the Whistle Blower," which appeared in the *North Carolina Medical Journal* last September (NCMJ 1984;45:567-75).

I am so touched by your article that I would like to reprint it in the fall issue of *Alumni News*. I request permission to do so.

Your article is so personal and so revealing. What you have experienced will be of great value to our alumni readers. Bless you for demystifying chemotherapy in such an open manner — and with such good-hearted charm. I rejoice with you that the outcome of your treatment has been positive.

Miriam Holland
Editor, *Alumni News*
UNC, Greensboro
Greensboro 27412

Questionable Medical Advertising

To the Editor:

Dr. Maymandi, M.D., Chairman of the State Medical Committee on Ethics, has informed me that he has taken it upon himself to inform each one of you of an ad that appeared three times in the Fayetteville newspaper, *The Fayetteville Times*, in Fayetteville, NC, concerning the opening of a mammography imaging center located at a Doctor's Urgent Care Centre facility in Fayetteville, NC. Although I do not have direct involvement at this time with the imaging center and did not have prior knowledge of this advertising modality, I am the Medical Director for Doctor's Urgent Care and feel that I must respond to the advertisement, as well as to Dr. Maymandi's letter to you.

It was, for me, a most unhappy experience to see this form of advertisement in the paper. I immediately contacted Mr. Sid Wolinsky, who is the President of Doctor's Urgent Care Centre, and informed him of my deep concern that the ad, with the schematic drawing of the lady, would appear to be in very poor taste and placed in the paper with poor judgment. Mr. Wolinsky immediately agreed and stated that he also had not had the opportunity of seeing this material before publication. We have had a board meeting concerning this advertisement, and our board has been equally unhappy. Unfortunately, because the advertisement does represent our imaging center, we must assume the responsibility. I would like to explain how this happened but realize that the blame must certainly be ours.

An excellent radiologist, Dr. Martin Locey, M.D., directs the new imaging center at a facility managed by Doctor's Urgent Care Centre. I personally know him to be one of the finest trained radiologists I've had the pleasure of meeting. As part of the imaging package, a mammography unit was established, and Dr. Locey has put together a patient educational program for self-examination with encouragement to seek annual examinations by their own physicians. This educational experience is accompanied by the newest mammography equipment available with the lowest yield of radiation. It was felt that this was a service needed in our community, as mammography had been offered by the only radiological team in the area at $150.00 per examination. They have subsequently reduced their fee to $75.00, and I can only feel that this was a result of the competitive nature of this center.

An advertisement agency was hired to announce to the public the establishment of the mammography clinic. They put together the advertisement that you have seen, and unfortunately, no one on the Doctor's Urgent Care Centre staff saw the ad prior to it being placed in the paper. Apparently, the business component division felt that the professional component was handling this, and the opposite also had been thought to be true, but apparently not so. When the ad came out, we did have our meeting, and it was requested to withdraw the ad from the paper. Unfortunately, the ad was going to be in a Sunday edition and that section of the paper had already been printed; therefore, it was unable to be withdrawn, so a second ad appeared. The advertisement company was contacted and told the ad was not felt to be appropriate, particularly the schematic drawing. The final insult to the situation was that the advertising people did change the schematic, but certainly not enough to make the ad tolerable, and their change went into the paper as the last and final advertisement.

This ad has been entirely and totally withdrawn from the paper, and I can assure you future publicity will be looked at closely by the medical staff of Doctor's Urgent Care

Centre. It is my hope that a better understanding of the center and the need for the center and who should and should not take advantage of this clinic will be spelled out in the information. In no way does the Doctor's Urgent Care Centre want to capitalize on any form of scare technique, but with breast cancer being such a significant illness in the female population, we wish to do all we can to aid in the early detection of the disease that may result in a higher percentage of cures.

We are extremely upset that this advertisement appeared, since it is our goal to address this clinic to the public in the most professional manner; and rest assured that the proper mechanism has been set in place to be certain that our advertising service follows accepted professional advertising standards.

Arlyn M. Moeller, M.D.
Medical Director
Doctor's Urgent Care Centre
Fayetteville 28304

Editors' response:

This is a good example of problems we'll be encountering in corporate medicine, when the left hand doesn't know what the right hand is doing.

On Asparagus

A number of years ago I shook the innermost circles of science with a scholarly study of the heritability of wool distribution patterns in the faces of Hampshire sheep. (From whence that beard?) Naturally, I was fascinated by the asparagus paper by Sugarman and Neelon in the June NCMJ (1985;46:332-5). Important questions deserve thoughtful study.

The authors make some interesting observations and suggest another question. Is the stirring up of lust a variable, and if so, how? Is excretion vs non-excretion or is perception vs non-perception the key? The composition of the study group suggests that some further objective as well as subjective observations are conceivable.

One of my colleagues at Granville County Hospital is a non-perceiver. I don't know about excretion, nor am I likely to find out.

William B. Tarry, Jr., M.D.
104 New College Street
Oxford 27565

Isolated ACTH Deficiency

To the Editor:

We were really interested by the report on ACTH deficiency published in your journal (NCMJ 1984;45:632-5) because we also work on the problems of hypocorticismus. The review provokes some questions which we want to discuss with you.

1. It seems to us that the title does not reflect the essence of the report. In fact the cases reported do not concern a real "isolated ACTH deficiency," but ACTH deficiency in general. The described clinical data are a result of different pathological processes, not only of an "isolated ACTH deficiency."

2. In the first case reported you describe a normal blood level of ACTH and low cortisol. The authors accept an "isolated ACTH deficiency" only on the basis of a 3-day suprarenal stimulation, but there was not any stimulation test of the pituitary (hypoglycemia or vasopressin test). The authors would have been more successful in reporting the case if they had made one of the mentioned tests and had described the levels of ACTH and cortisol after the test. It is not sufficient to do only a 3-day ACTH stimulation to decide whether the adrenal deficiency is primary or secondary. We have had cases with primary suprarenal insufficiency who have increased the level of cortisol after a Synacthen stimulation. We think that computer tomography can also play a significant role in the diagnosis of the case.

3. In the reported case with subtotal gastrectomy, atrophic gastritis, syphilis and macrocytic anaemia there were results of the insulin stimulation test but there was not the ACTH level after the test. We suggest the following possible diagnosis:

a) A subtotal gastrectomy with atrophic gastritis and malabsorption syndrome and, as a result of this, insufficiency of the endocrine system as a whole with heavier damage in the function of the suprarenal glands and hypophysis. (Here the levels of FSH, LH, Prolactin, TTH, ACTH were not present.)

b) An atrophic gastritis due to an autoimmune mechanism, which has affected the suprarenal glands. (We need data about autoantibodies against different organs, especially against the suprarenal glands.)

c) Adrenal insufficiency as a result of the syphilis (directly or indirectly). To support this suggestion we need computer tomography.

4. In reported case 3 there is an autoimmune mechanism with a coexistence of pathological processes of the hypophysis, thyroid and suprarenal glands. Here it would be of great significance for the diagnosis to evaluate the lack or existence of antiadrenal autoantibodies in order to differentiate whether there is a primary or secondary hypocorticismus. Computer tomography would help in the diagnosis of this case.

Ivan Krestev
Tsvetanka Terzieva
Medical Academy
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The authors respond

To the Editor:

Drs. Krestev and Terzieva have submitted an interesting letter.

1) The term "isolated ACTH deficiency" denotes a monotropic deficiency of the pituitary-hypothalamic secretion of ACTH. In other words, no other pituitary hormone is compromised. It does not imply that the deficiency will occur in the absence of any other illness. In addition to presenting many of the characteristic signs and symptoms of hypocortisolism, these patients can present with symptoms of any other associated illness.

2) The bases for the diagnosis of isolated ACTH deficiency in the first case were a) the low cortisol levels with simultaneous low normal ACTH levels. (In primary adre-

nal insufficiency there is low cortisol and high ACTH levels.) b) low 17 OH-cortisosteroids, urinary free cortisols and serum cortisol that increased stepwise during three days of intravenous ACTH stimulation.

We do not understand the claim of Drs. Krestev and Tersieva of having cases of "primary suprarenal insufficiency who have increased the level of cortisol after synacthen stimulation." This, by definition, would invalidate the diagnosis of primary adrenal insufficiency.

3) The different theoretical possibilities mentioned for patient No. 2 are doubtful because of the normal thyroid hormone, testosterone and prolactin levels. Again, one cannot postulate primary adrenal insufficiency in a patient who shows a normal cortisol response to ACTH. This together with failure to increase the cortisol level during symptomatic hypoglycemia has to be interpreted as a deficiency in ACTH secretion. It is possible that the underlying mechanism is an autoimmune one.

4) We agree that in case 3 there is an ongoing autoimmune process. We do not have definite proof that this autoimmune process involves any other organ than the thyroid. The presence of any adrenal antibodies would suggest an autoimmune attack to the adrenals, but would not be of help in deciding if the patient had primary or secondary adrenal insufficiency. This is a functional diagnosis. The ACTH stimulation, the insulin tolerance and metyrapone test all suggest that the hypocorticism is caused by ACTH deficiency.

Finally, we think that computerized tomography is an excellent technique to visualize the adrenals. Unfortunately it does not provide any information about the function of the adrenal glands.

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Emil E. Werk, Jr., M.D.
New Hanover Memorial Hospital
Wilmington 28402

Ole Doc

Recently a fellow physician agreed that we have been privileged to practice through what seems to be the final days of the best days of the practice of medicine despite the many new developments in drugs and marvelous procedures. Nevertheless, reflecting upon this, these lines came to me:

His rickety buggy
Down the muddy road he rode
His patient's pain to ease
Now he has other things
To worry about
Not only patient
But family, lawyer,
Uncle Sam and PISRO to please.

There was a time when doctoring was more fun
When the horse, not the doctor, stayed on the run
When Ole Doc received thanks with respect
Even when his treatment failed
Twas still the horse — not Ole Doc —
Who got the whip to the tail.

John Fitzgerald, Jr., M.D.

AFTER BREAKTHROUGH BLEEDING AND AMENORRHEA...
SHE'S ABOUT TO GIVE UP ON ORAL CONTRACEPTION.

NORLESTRIN®

(1 mg norethindrone
acetate and 50 mcg ethinyl
estradiol tablets,
USP) 1/50

BECAUSE SOMETIMES A 50 IS PREFERABLE.

See next page for brief summary of prescribing information.

Brief Summary of Prescribing Information
NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information A Brief Summary follows

DESCRIPTION
Norlestrin Products are progestogen-estrogen combinations

INDICATIONS AND USAGE
Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0 05 per 100 woman-years; in clinical trials with Norlestrin 2 5/50 involving 96,388 cycles, there was a pregnancy rate of 0 22 per 100 woman-years

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance

CONTRAINDICATIONS
1 Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3 Cerebral vascular or coronary artery disease
4 Known or suspected carcinoma of the breast
5 Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding
7 Known or suspected pregnancy (See WARNING No 5)
8 Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

WARNINGS
Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1 *Thromboembolic Disorders and Other Vascular Problems* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2 0 times greater in users than nonusers, and the risk of thrombotic stroke was 4 0 to 9 5 times greater

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not Oral contraceptives, however, were found to be a clear additional risk factor

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders Should any occur or be suspected, the drug should be discontinued immediately

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization

2 *Ocular Lesions* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions

3 *Carcinoma* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives Close clinical surveillance of users is, nevertheless, essential In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms, should be monitored with particular care

4 *Hepatic Tumors* Benign hepatic adenomas have been found to be associated with oral contraceptives Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives The relationship of these drugs to this type of malignancy is not known at this time

5 *Usage in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring* During early pregnancy, female sex hormones may seriously damage the offspring

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy

6 *Gallbladder Disease* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives

7 *Carbohydrate and Lipid Metabolic Effects* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed

8 *Elevated Blood Pressure* An increase in blood pressure has been reported in patients receiving oral contraceptives The prevalence in users increases with longer exposure Age is also strongly correlated with development of hypertension Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure

9 *Headache* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives

10 *Bleeding Irregularities* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives In breakthrough bleeding, nonfunctional causes should be borne in mind In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives

11 *Ectopic Pregnancy* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures

12 *Breast-Feeding* Oral contraceptives may interfere with lactation Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs

PRECAUTIONS
1 A complete medical and family history should be taken prior to the initiation of oral contraceptives The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2. Preexisting uterine leiomyomata may increase in size

3 Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

4 Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated

5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued

6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.

7 Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency

8 Serum folate levels may be depressed

9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted

10 Certain endocrine and liver function tests and blood components may be affected

(a) Increased sulfobromophthalein retention (b) Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone (d) Decreased pregnanediol excretion (e) Reduced response to metyrapone test

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives thrombophlebitis, pulmonary embolism; coronary thrombosis; cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma, breast changes, change in weight, change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine; increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature, intolerance to contact lenses

The following adverse reactions have been reported and the association has been neither confirmed nor refuted premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome; headache, nervousness; dizziness; hirsutism; loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption; vaginitis, porphyria

Special Notes on Administration
Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication

After several months on treatment, bleeding may be reduced to a point of virtual absence; reduced flow may be a result of medication and not indicative of pregnancy

HOW SUPPLIED
Norlestrin $\boxed{21}$ 1/50 is available in compacts each containing 21 tablets Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{21}$ 2 5/50 is available in compacts each containing 21 tablets Each tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{Fe}$ 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{FE}$ 2 5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets Each pink tablet contains 2 5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Each brown tablet contains 75 mg of ferrous fumarate, USP Available in packages of five compacts and packages of five refills

Norlestrin $\boxed{28}$ 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol Available in packages of five compacts and packages of five refills

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NORTH CAROLINA MEDICINE TODAY

Aging in its many aspects

It is estimated that 25 million people (11% of the population) are over age 65, and represent the fastest-growing segment of the population by far. It is further estimated that this group currently spends approximately 75 billion dollars annually for personal health care, and accounts for some 55% of all federal health dollars.[1] For these reasons alone, studies concerned with various aspects of aging are of vital importance to the entire nation. Much major research in this complex area is being conducted in North Carolina, at its several medical centers and universities, often under grants from the National Institute on Aging.

Studies cover a wide range

Recent studies have reported on the physiological dynamics of aging as related to circulatory diseases and circulatory risk factors at advanced ages (over 85) as compared to findings in a study population with a mean age of over 70 years.[2] Another study, stemming from the comprehensive Duke First Longitudinal Study, evaluated Wechsler Memory Scale scores as related to distance from death and the potential use of the WMS as a predictor of survival in both normal and demented elderly populations,[3] while yet another compared young and old adults in the spontaneous use of context to learn and recall information.[4]

Dealing with America's fourth leading killer disease

Researchers at Duke University Center for the Study of Aging are focusing on the study of Alzheimer's disease, a type of primary neuronal degeneration that is the most common form of dementia. Estimates vary but indicate that as many as 4 million older Americans[1] are afflicted with this illness, which has been labeled "the disease of the century."[5] Concurrent with its medical research on Alzheimer's disease, the Duke University Center is providing innovative support mechanisms for afflicted families and other caretakers. A hotline provides callers with telephone consultations, introductions to others close by in similar circumstances, and practical medical, legal and psychological information. The Center has also aided in the establishment of 19 local support groups statewide, and regularly makes available information on Alzheimer's disease to health providers, nursing homes and hospitals, and others responsible for programs and services directed toward the victims of this killer disease.[6]

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

> ***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

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Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

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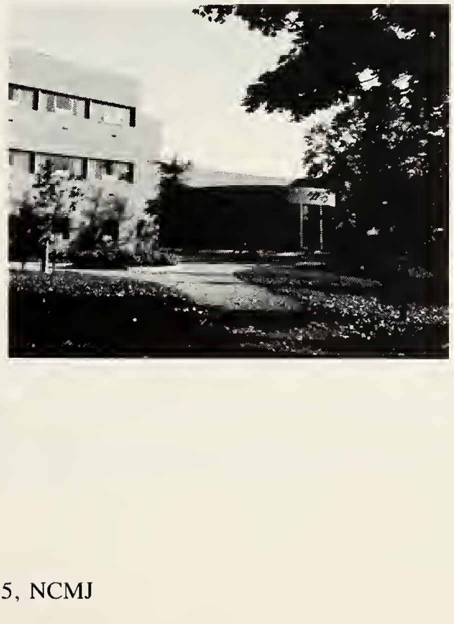

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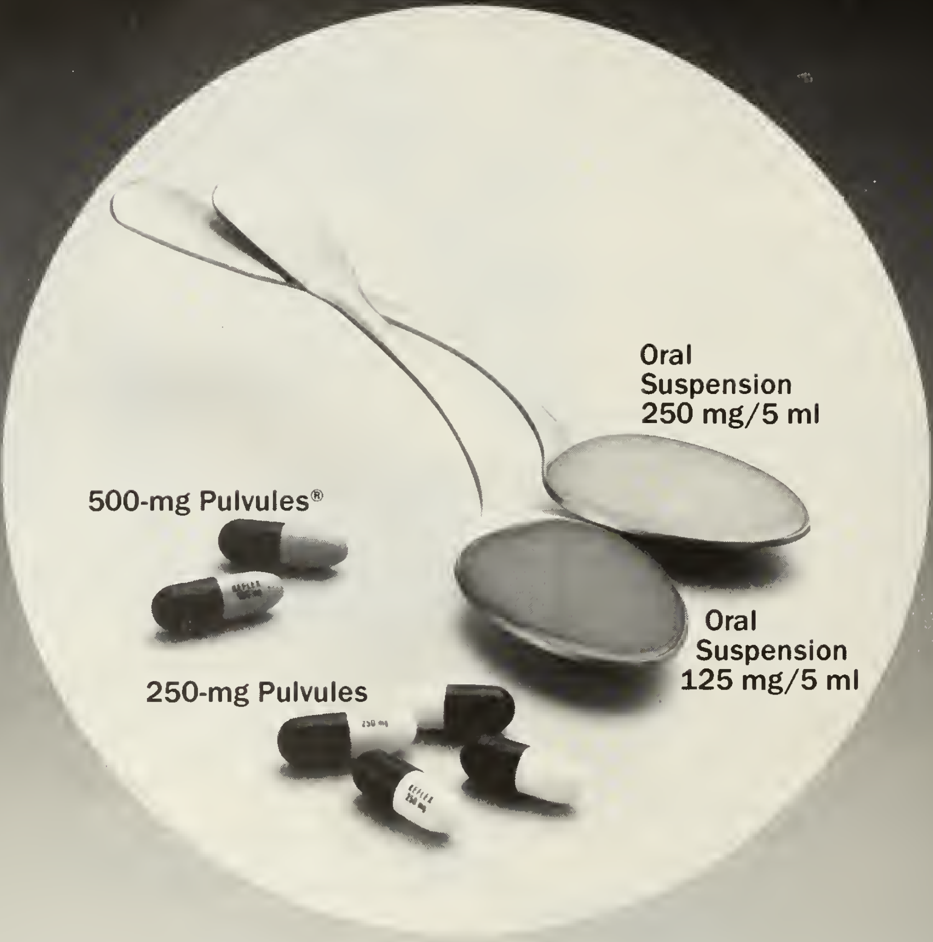

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LEARNING WITHOUT WORDS

That Addisonian Tan: The Healthy Looks that May Deceive

Mark Linzer, M.D.

- *A man from Buffalo who feels poorly, craves salty foods, and looks in December as if he just stepped off the beach — but didn't — must be viewed with a skeptical eye.*

"WHAT a tan!" The phrase can be heard frequently around the swimming pools, backyards, and beaches of North Carolina. But physicians have become increasingly aware that solar energy can produce serious and long-lasting destructive dermal and epidermal changes as well as markedly increase the risk of developing malignant melanoma. Thus, the medical literature has recently been filled with warnings for our patients to wear protective clothing, utilize sunscreens and even beware the reflection from sand, snow or water.

With the plethora of recent reminders concerning the evils of suntanning, physicians may begin to view the excessively tanned person as someone not unlike the chronic smoker — individuals who merit a serious lecture on the dangers of their "habit." The following case report will serve as a reminder that excessive suntanning may be a sign of the life-threatening but treatable disorder described by Thomas Addison 130 years ago; it illustrates that a patient with this disorder may appear deceptively healthy.

I recently saw a 27-year-old former carpenter who complained of two months of weakness, anorexia, nausea, dizziness and a 10 pound weight loss. He also noted that his suntan from the previous summer had not faded. In fact, he felt that his tan was even darker in December (while he was living in Buffalo) than it had been the previous July. Over the past six months he had developed a craving for Doritos such that he consumed over one large bag (containing

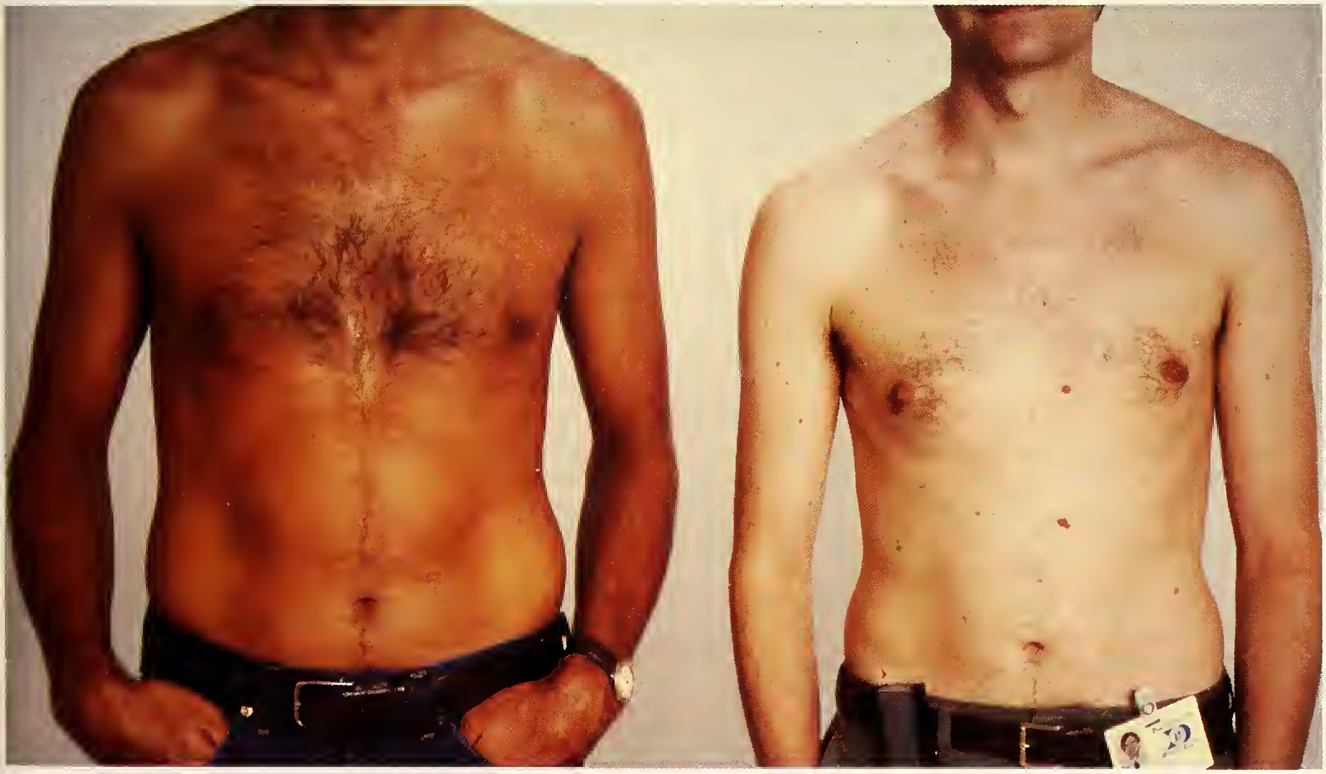

Figure 1. *Patient (on left) with excessive hyperpigmentation. Author's chest is included for comparison.*

From the Department of Medicine, Duke University Medical Center, Durham 27710.

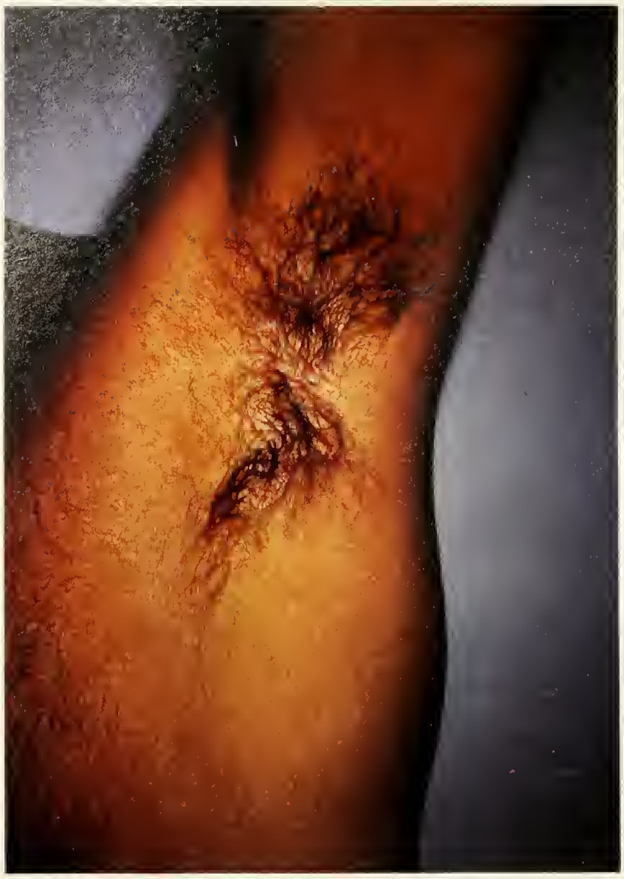

Figure 2. *Patient's suntanned axilla.*

approximately 4 g of sodium) per day. The patient had had no trauma, recent surgery or exposure to tuberculosis. He had always been in good health before the present illness. The family history was remarkable for hypothyroidism in his mother and adult onset diabetes mellitus in an aunt. He was a tall, healthy appearing, lean and muscular person with a dark tan that was most prominent in sun-exposed areas (figure 1). The tan was sharply demarcated at the line where he wore his swimsuit. There was no hyperpigmentation of the palms or buccal mucosa, and no accentuation of tanning at the elbows, knees or metacarpophalangeal joints. There was some excessive tanning in the axillae (figure 2).

His blood pressure was 110/80 supine and dropped to 90/60 while standing. His heart rate was 80 supine and 108 standing. He was afebrile and breathing comfortably at rest. Cardiac examination showed normal heart sounds with a mid-systolic click. Due to the combination of orthostasis and the excessive tanning, the diagnosis of Addison's disease was considered. This diagnosis was supported by finding that the serum sodium was 121 mm/l (normal 135-145 mm/l) and the potassium was 4.9 mm/l (normal 3.2-4.7 mm/l). Serum glucose was 76 mg/100 ml (normal 75-100 mg/100 ml).

The patient was placed in the hospital for further diagnostic evaluation, including a 48 hour cosyntropin stimulation test. Although a ''one shot'' cosyntropin stimulation test might have been sufficient in the eyes of some, I performed the full 48 hour test in order to unequivocally document a diagnosis which, once made, would relegate the patient to a lifetime of medications for an endocrine insufficiency disease that is potentially life threatening.

A morning serum cortisol was markedly low at 4.8 μg/dl (normal 12-25 μg/dl) and a simultaneous ACTH level was elevated at 121 pg/ml (normal 10-50 pg/ml). Continuous cosyntropin stimulation produced no rise in serum cortisol after 48 hours (normal response = $>$ 50 μg/dl). A skin test for tuberculosis was negative at 48 hours, and an abdominal CT scan showed no evidence of metastases, calcification, or adrenal hemorrhage. A diagnosis of primary adrenal insuficiency was made, and the patient was started on cortisone acetate and fludrocortisone by mouth. After only two weeks the patient was feeling markedly improved. There a sharp decrease in his consumption of Doritos, and his tan had already begun to fade.

From Addison's original description of his patients with adrenal failure, one might not expect the vigorous, suntanned appearance of the patient reported above to be a sign of Addison's disease. Indeed, the ''anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and peculiar change of color in the skin'' noted by Addison,[1] might lead one to expect a sallow and debilitated individual. Although my patient felt unwell, there was nothing in his general appearance that gave a clue to this. Perhaps this is why he waited so long before seeking medical attention. Not all patients with Addison's disease are hyperpigmented,[2] but the vast majority are excessively tanned,[3] often in unusual locations. In our patient, the tanning in the axillae (especially during a Buffalo winter) was a clue that pathologic tanning was taking place. The association of mitral valve prolapse with Addison's disease has not previously been reported and at present can only be viewed as a chance association.

Chronic sunlight exposure is associated with several dermatopathologic changes including wrinkles, telangiectasiae, Favre-Racouchot Syndrome (yellow facial skin color with cysts and comedones) and the poikiloderma of Civatte (prominent hair follicles in brown telangiectatic skin). Excessive suntanning, while clearly a common sign of longstanding exposure to ultraviolet light, should also raise the specter of primary adrenal insufficiency, even in the ''glowingly'' healthy patient.

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Triiodothyronine Therapy: An Iatrogenic Bait

Jorge J. Gonzalez, M.D.

• *There are thyroid pills and thyroid pills.*

THE alterations of the classical thyroid function test produced by T3 replacement or suppression therapy are well known. Despite this fact continued misinterpretation of the results of thyroid function tests of patients on T3 therapy occur. Some patients do not know the type or name of their thyroid pills. The following exchange illustrates the history of several patients I have seen in the last two years.

"How long have you been taking the thyroid pills, Ms. Smith," asked Doctor One. "Oh, three or four years," said Ms. Smith. "Do you know why you were started on the thyroid pills?" Doctor One asked. "The Doctor told me my thyroid was low or something like that," replied Ms. Smith. "Well, we'll check that out," said Doctor One.

Two days later T4 is 2.0, free thyroxine index equals 1.3 (those values are quite low). Phone call: "Ms. Smith, are you taking your thyroid pills?"

"Yes, Doctor One, every day," she said. "Well, your blood levels are very low so double your tablets, okay?" retorted Doctor One.

One month later Ms. Smith is talking to Doctor Two: " . . . and my thyroid level was very low so he told me to double my pills. I still feel quite bad, as a matter of fact, worse." Thyroid functions are checked again. T4 is now less than 1. Doctor Two phones Ms. Smith. "Are you taking your pills, Ms. Smith . . . ?"

Ms. Smith ends on a fairly massive dose of triiodothyronine (Cytomel) replacement and with a beautiful case of iatrogenically-induced hyperthyroidism.

The classical "thyroid function test" used in the great majority of hospitals and private offices includes a total T4, a T3 resin uptake and a free thyroxine index. Ingestion of triiodothyronine in doses greater than 50 μg per day suppresses TSH secretion by the hypothalamus-pituitary complex. This suppression of the TSH induces a marked hypofunction of the thyroid gland. (This was recognized quite

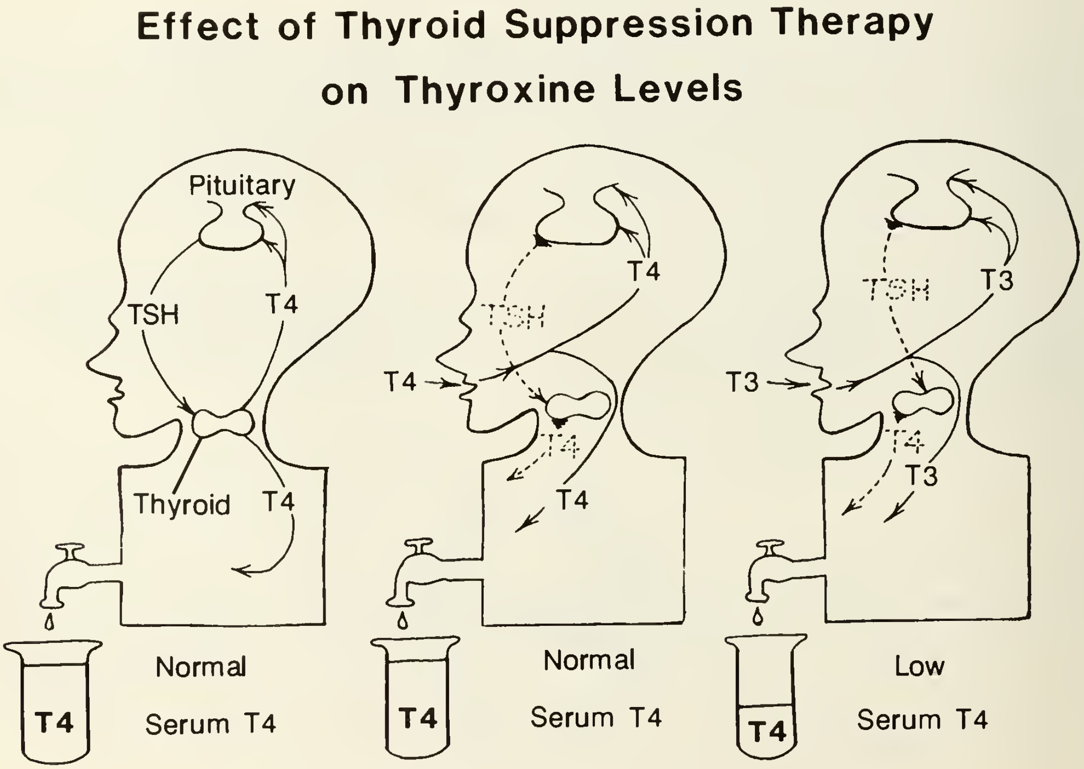

Figure 1. *A simplified scheme of thyroid suppression by T_3 or T_4.*

From the Department of Internal Medicine, New Hanover Memorial Hospital, Wilmington 28402.

early and was the basis for the now somewhat displaced "thyroid suppression test.") The hypofunction of the thyroid gland produces a marked decrease in the circulating T4 level (figure 1). Neither the total T4 nor the resin uptake measure the circulating T3. The conventional package of thyroid function tests will show numbers that will suggest hypothyroidism. If the treating physician is not aware of the exact type of thyroid pills the patient is taking, he may commit the mistake of asking the patient to increase the triiodothyronine. The increase of the dose of T3 is followed by a more profound depression of the T4 level and, too frequently, an additional increase of the "thyroid replacement."

Patients on T3 replacement or suppression therapy should be followed using measurements of T3 by radioimmunoassay, TSH, and in some cases TRH stimulation tests.

So next time you see a patient on "thyroid pills" with a low total T4, ask her or him to look at the prescription bottle. You may be in for a surprise!

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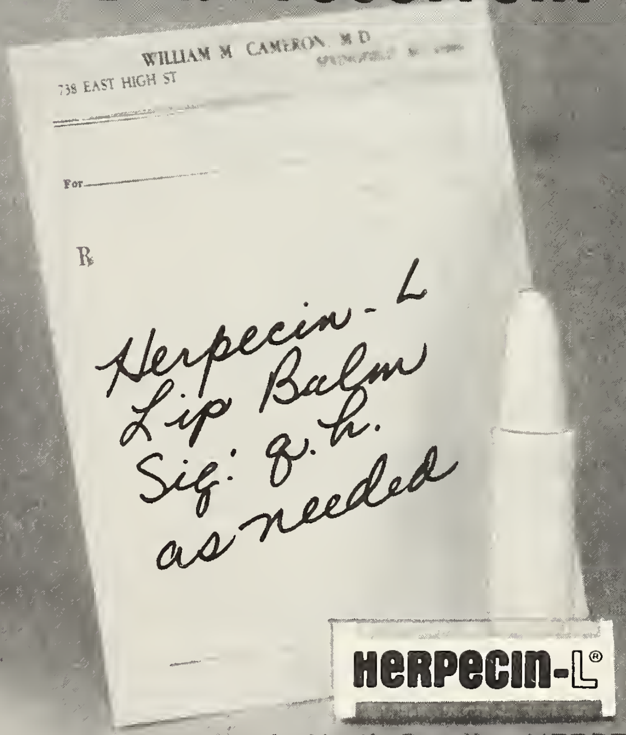

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SCIENTIFIC ARTICLE

Overwhelming Infection After Splenectomy: A Challenge to Preventive Medicine

Johnny B. Craig, M.D. and Bayard L. Powell, M.D.

• *This is a case of overwhelming post splenectomy infection from which the patient died 20 years after removal of her spleen.*

SPLENECTOMIZED patients are at increased risk for infections; the most dramatic and clinically significant is overwhelming post splenectomy infection (OPSI), a syndrome of documented bacterial septicemia and/or meningitis more than six weeks after splenectomy.

A 67-year-old white woman presented after three days of nonproductive cough, myalgias, and malaise. Twenty-four hours before admission she had noted fever of 102° F, a shaking chill, nausea, vomiting, diarrhea, and discoloration of the skin of her face, hands and feet. She was treated with intravenous ampicillin and tobramycin in the referring emergency room and transferred to our institution. Her spleen had been removed 20 years earlier because of trauma.

Upon arrival she was alert and oriented, but tachypneic, febrile (oral temperature 102.5°F) and hypotensive (70/30 mm Hg) with generalized purpura and ecchymoses. White blood cell (WBC) count was 20,300/mm with 56% segmented neutrophils and 31% band forms. Dohle bodies (pale blue intracycloplasmic inclusion bodies) were noted and intracellular encapsulated diplococci were obvious within WBCs on routine blood smear. Urine and serum counter immunoelectrophoreses were positive for Streptococcus pneumoniae. Prolongation of the prothrombin time (38.9 seconds), partial thromboplastin time (>120 seconds), thrombocytopenia (46,000 mm^3), hypofibrinogenemia (26 mg/dl) and elevated fibrin split products (>256 and <512 μg/ml) consistent with disseminated intravascular coagulation were all present. Arterial blood gases revealed hypoxemia and a profound metabolic acidosis (ph 7.34; pCO_2 22; pO_2 53; HCO_3 11.3).

Despite aggressive respiratory, cardiovascular (volume replacement and vasopressor agents), chemotherapeutic (high dose penicillin, high dose steroids), and hematologic (platelet, red blood cell, and fresh frozen plasma transfusion) therapy, the patient rapidly deteriorated and died 36 hours after admission. Premortem blood cultures were positive for pneumococci exquisitely sensitive to both penicillin-G and ampicillin. Autopsy findings were consistent with septicemia, disseminated intravascular coagulation, and adrenal hemorrhage.

Discussion

This case is a definitive example of the dramatic presentation and clinical course associated with overwhelming postsplenectomy infection. The incidence of this syndrome is related to age, interval after splenectomy, and the presence or absence of an underlying medical illness. The overall mortality from sepsis in splenectomized patients is 30-200 times higher than in a population with normal splenic function.[1-3] OPSI is most common in the pediatric population with the majority of cases (70-80%) occurring within three years after splenectomy; however, cases occurring up to 31 years postsplenectomy have been reported.[1, 3-5] Children whose spleens are surgically removed before 12 months of age have the greatest chance of developing OPSI; risk gradually decreases until age 17 after which the incidence is relatively independent of age (0.5-2.0%).[1, 3, 4, 6, 7] In children the risk of developing OPSI is increased in those with an underlying hematologic or malignant disease when compared with patients with splenectomies after trauma. The highest risk in this population occurs in association with thalassemia (16-25%) and lymphoreticular neoplasms (9.5-11.5%); the lowest after trauma-related splenectomy (1.5-2.1%)[1, 3] In contrast to the pediatric population, in adults the syndrome is less common, occurs more than 3 years after splenectomy in up to 75% of cases, and incidence shows little correlation with age or underlying disease.[1, 7]

The clinical syndrome is most frequently caused by encapsulated bacteria; pneumococcal infections are the most common (50-60%). However, Hemophilus influenzae, Neisseria meningitidis, staphylococci, Salmonellae, Escherichia coli, Pseudomonas aeruginosa, other streptococcal species, and Listeria monocytogenes have been reported to be the causal organism in case reports.[1-7] There is often a prodromal period characterized by symptoms similar to those of "viral syndromes" for 36-72 hours before the onset of the acute fulminant illness described in our patient. The fulminant illness is characterized by disseminated intravascular coagulation in greater than 50% of cases (especially in cases caused by pneumococcal organisms), Waterhouse-Friderichsen syndrome (50%) and visible organisms on peripheral smear (33%). The mortality rate is 50-80% despite appropriate therapy. Recurrences are common among survivors (40-50%).[1-4]

From the Department of Medicine, Bowman Gray School of Medicine, Winston-Salem 27103.

The mechanism of increased susceptibility to overwhelming infection in patients after splenectomy is multifactorial.[1-3, 8, 9] The spleen is the major source for sequestration of non-opsonized bacteria, a role which is especially vital for encapsulated organisms that are inherently resistant to phagocytosis. In addition, there is delayed production of opsonizing antibody to bacteria in this group of patients; therefore clearance of bacteria by the liver and the rest of the reticuloendothelial system is delayed. The spleen is also the major producer of IgM, the most effective immunoglobulin in opsonization of encapsulated organisms and the storage site of helper T lymphocytes.

Since up to 80% of OPSI patients die despite appropriate therapy, prevention is vital. Pneumococcal and meningococcal vaccines should be administered to all splenectomized patients, preferably as much as one month prior to surgery. Since not all pneumococcal serotypes are included in these vaccines and splenectomized patients have evidence of a quantitatively smaller and chronologically shorter specific antibody response, vaccination alone is insufficient for adequate protection.[2, 8, 10, 11] All authorities agree that extensive patient education with instruction to take 1-2 grams of ampicillin and seek medical advice immediately upon onset of prodromal symptoms is indicated for all patients who have undergone splenectomy. Penicillin prophylaxis (125 mg for children or 250 mg for adults two times per day), though not evaluated in randomized controlled studies, is recommended for all patients during the 3-5 years after splenectomy, for patients with low antibody titers after pneumococcal or meningococcal vaccines, and for those with other high risk states (e.g., patients with high job exposure or undergoing immunosuppressive therapy).[1, 8, 12] The ultimate in prevention is the avoidance of splenectomy whenever possible. This can be accomplished by using splenorraphy instead of splenectomy when feasible after trauma, by limiting staging splenectomies (as in Hodgkin's disease) to only those cases where therapy will be changed by the surgical findings, and by delaying elective splenectomies in children until they reach an age of lower risk.[1, 3, 7, 8]

Infectious complications other than OPSI also appear to be more common in splenectomized patients; these include immediate postoperative infection, herpes zoster infections in patients with Hodgkin's disease, malaria and babesiosis.[1, 3]

Our patient exhibited the most common features and the fulminant clinical deterioration associated with the syndrome of OPSI in an otherwise healthy patient 20 years after splenectomy. Since therapy is largely ineffective once this syndrome is clinically evident, prevention must be stressed in all splenectomized patients.

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Snakebite Treatment in the 80s

Theodore R. Winneberger, M.D., E. Jackson Allison, Jr., MD/MPH, Joyce M. Mitchell, M.D.,
Mark R. Pierce, M.D., George Podgorny, M.D. and J. Jeffrey Tope, M.D.

- *This paper outlines the sensible steps to take, and some of the controversies, when a victim encounters a poisonous snake.*

SNAKE envenomations, although not a frequent event in most physicians' medical practices, are nonetheless a medical emergency requiring an organized approach to treatment for a successful outcome.

In the U. S., approximately 8,000 people are bitten each year, and 12-15 of these result in death.[1] North Carolina has been found to have the highest incidence of poisonous snake envenomations; they occur here at a rate of 18 cases per 100,000 of the population.[2]

There are 20 species of poisonous snakes in the U. S., the majority of which are pit vipers (crotalids) which include the rattlesnakes, copperheads and water moccasins. Another group, the elapidae, includes the coral snake, which will be discussed later in this paper.

Poisonous snakes are endemic in every state except Maine, Alaska and Hawaii. Identifying features of the pit vipers include the pit between the eye and nostril bilaterally. This is apparently a heat-sensing organ used in finding prey. Pit vipers have triangular-shaped heads and elliptical pupils if you get close enough to observe them. On their underside, they have a single row of caudal plates, most safely observed when the snake is dead. Pit vipers deliver their venom through fangs supplied by venom glands, each of which has an individual muscle and nerve. This system allows the snake to inject variable amounts of venom or none at all. Of individuals bitten by crotalids, up to 30% may not have been envenomated.[3, 4]

In North America bites are predominantly inflicted by the crotalids and rarely by the elapidae.[5] Other more rare poisonous snakes in North America will most likely be found in the zoo where identification is already known. Distinguishing which snake has inflicted the bite should be straightforward, and treatment with antivenin will consist of a single antivenin for the crotalids and a single antivenin for the elapidae, removing much confusion about which antivenin should be used.

The pit viper's striking range may be as much as one-third to two-thirds of its body length. Some rattlesnakes have been known to attain lengths of seven to eight feet, and anecdotes have reported them over nine feet long. Rattlesnakes account for most of the mortality and morbidity from envenomations.

The copperheads are reportedly the least poisonous of the pit vipers, with some authors stating that the treatment of copperhead envenomations should be undertaken only in the young, the old and the chronically ill.[6] Most experts would recommend simple observation of other patients except in the case of apparently significant envenomation. Pit viper venom is very destructive to mammalian structures.[3, 7-9]

Clinical manifestations of envenomations can vary, but the most common initial reaction is burning pain followed by localized tissue swelling. Some of the more common systemic symptoms include nausea, vomiting, paresthesias, hypotension and muscle fasiculations. The deaths that occur secondary to envenomations are not infrequently due to coagulopathies.

Treatment

Prehospital treatment has been the subject of much discussion and controversy for a number of years. After being bitten, the first thing to do is to move away from the snake. Some authors recommend killing and bringing the snake in for identification;[10] since few people have any experience in handling snakes, however, this does not seem to be wise. Bites have been known to occur even from a disembodied head.

Another commonly recommended procedure in prehospital care of snake envenomations is incision and suction, popularized in the 1920s and restudied several times in more recent years. The more recent literature suggests that if the patient has signs and symptoms of envenomation, if transport to a hospital will take longer than an hour, and if the procedure can be performed safely without damage to underlying structures, then it should be done.[9, 10] It is doubtful that this recommendation is safe for the lay public, most of whom have never cut another human therapeutically. Incision and suction has been shown to remove some of the venom from the wound and some victims having it performed tend to have a less severe reaction to their bite.[11-13] Incision and suction should be done 15 minutes after the bite and continuous suction should be applied for 30 to 45 minutes.[3, 4, 14, 15] The incisions should be shorter than one centimeter, just through the subcutaneous layer, and across the bite marks. Incision and suction should only be used if the patient is showing signs of significant envenomation, is more than an hour from the hospital, and if the person to perform the procedure is comfortable doing it.

From the Department of Emergency Medicine, East Carolina University School of Medicine, Greenville 27834.

The use of a tourniquet is a controversial first aid recommendation. While the tourniquet has fallen into disfavor, the new terminology being used is that of "a loosely constrictive band" to occlude only the lymphatics. Many authors believe that the venom is disseminated via the lymphatics and that slowing its dissemination will lessen the severity of the patient's reaction in the field.[3, 4, 9, 14] Some authors disagree with the use of any band, even "a loosely constrictive band," because the tourniquet can exacerbate the swelling and edema of the extremity and can quickly become even more hazardous secondary to progressive ischemia to that extremity.

Ice and cooling of the site of the bite is condemned by the vast majority of physicians because of increased morbidity in cases treated with ice.[14-16]

Commonly accepted recommendations, felt at least to do no harm and possibly to help in first aid, include immobilizing the affected extremity, keeping the patient from taking anything by mouth while transporting, and always being aware of the ABCs of resuscitation while en route.

Depending on location of the health care facility, the patient may be confronted with either of two schools of thought regarding definitive treatment. Most agree with starting at least one I.V. of a crystalloid solution and drawing routine labs including type and crossmatch, prothrombin time, partial thromboplastin time, fibrinogen, fibrinogen degradation products, platelets, complete blood count, creatinine and urinalysis. The most common disagreement concerns whether or not surgical treatment has a place in the management of snakebites. En bloc excision of the bite site and frequent, if not routine, use of fasciotomies were popularized by Glass and are supported by some authors in the current literature.[7, 17] Most clinicians today favor antivenin as the definitive treatment and only use fasciotomies in a documented compartment syndrome.[5, 18-20] Some authors concede that en bloc excision may have a place in snakebite treatment, but only under very selective and still controversial situations: when the bite has occurred within 30 minutes; when the patient is showing significant manifestations of envenomation; when the patient has a history of being allergic to the antivenin or has a positive skin test to the antivenin.[21]

The administration of antivenin is well-covered in Otten's article in the *American Journal of Emergency Medicine* and will not be restated here.[6] Once the decision is made to use antivenin, which is any situation where signs and symptoms of envenomation occur, enough should be used to arrest the signs and symptoms.[6, 21, 22] Finally, cover the patient with appropriate tetanus prophylaxis and use a broad spectrum antibiotic.[4, 23]

Coral snakes, which are members of the elapidae, require separate discussion from the crotalids due to their many differences. These snakes are usually small, shy, slender, and very colorful. To distinguish a coral snake from similar looking but non-poisonous snakes, such as the king snake, observe the arrangement of the colored bands on its main body. As the saying goes, "red on yellow, kills a fellow; red on black, venom lacks." These band characteristics are consistent only on the mid-body. Coral snakes can be found along the eastern seaboard as far north as North Carolina, and there is a Sonoran or Arizona coral snake found in the southwestern United States. The delivery system of the elapids' venom is much less efficient than the crotalids. The elapidae have much smaller fangs, which require the snake to hold on longer in order to envenomate the victim. The venom of the elapidae is very different from the crotalids, with the exception of the Mojave rattlesnake, and has been recognized as being primarily neurotoxic with systemic manifestations appearing five hours or more after the bite. The earliest manifestations may be cranial nerve dysfunction such as ptosis, slurred speech and mydriasis. Respiratory musculature is affected last and is the most frequent cause of death.

Because of the variable period between bite and systemic manifestations, and the seriousness of the sequelae, all suspected coral snakebite patients (also Mojave rattlesnake bites) should be admitted to the hospital and receive five vials of antivenin, even in the absence of symptoms.

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SCIENTIFIC ARTICLE

Neck Masses: Illustration of a Logical Approach

Eugene W. Linfors, M.D. and Francis A. Neelon, M.D.

PATIENTS with neck masses often present first to their primary care physicians. It is essential that these physicians be familiar with the best methods for evaluating neck masses. The selection of proper diagnostic tests and treatment is especially important in cases of cancer since inappropriate choices can have disastrous consequences. We offer three cases which illustrate important principles of diagnostic strategy for adult patients with a neck mass.

Case 1

A 61-year-old white woman, previously in good health, noted a slowly enlarging lump in her neck and mild fatigability for nine months. She denied any pain, erythema, warmth, dysphagia or hoarseness and there was no fever, chills or weight loss. She denied smoking, excessive alcohol intake, prior neck irradiation, exposure to asbestos, woodworking or leather tanning processes. Physical examination was normal except for a mass on the left side of the neck which could be seen, as well as felt, to push the left carotid artery and sternocleidomastoid muscle anteriorly while deviating the trachea to the right. The mass was very close to but palpably separate from a normal-sized thyroid gland. It was firm but not hard, non-tender, and could be moved from side to side and up and down. It did not move with swallowing. The carotid pulsation was greater on the left than the right, but the mass itself did not pulsate. There was no bruit. Careful examination of the head, eyes, ears, nose, tongue and pharynx revealed no other lesions. There were no palpably enlarged lymph nodes in the neck, supraclavicular, axillary, inguinal, or epitrochlear areas.

Our assessment at this point was that of a mass in the left anterior triangle very close to, but distinct from, the thyroid gland. Differential diagnosis included a glomus tumor, congenital cyst, thyroid neoplasm, or a metastatic tumor. An enlarged salivary gland or carotid aneurysm was considered unlikely as was cervical lymphadenitis.

Blood count and differential, serum chemistries, and chest x-ray were normal. Further definition of the extent of the mass as well as its site of origin and etiology were sought. Thyroid scan showed decreased uptake in the left lower pole but an otherwise normal gland. Computerized tomography demonstrated a mass which appeared to be within the carotid sheath but could not be distinguished with certainty as separate from a slightly enlarged left thyroid lobe (figure 1). It was markedly enhanced with contrast, suggesting its vascular nature. An aortic arch study and selective angiograms of the left carotid and thyroid arteries demonstrated a very vascular mass (figure 2), the blood supply to which arose from the left inferior thyroidal artery and to some extent from the left superior thyroidal artery. These imaging procedures had narrowed the differential slightly, but not much further than had the physical exam.

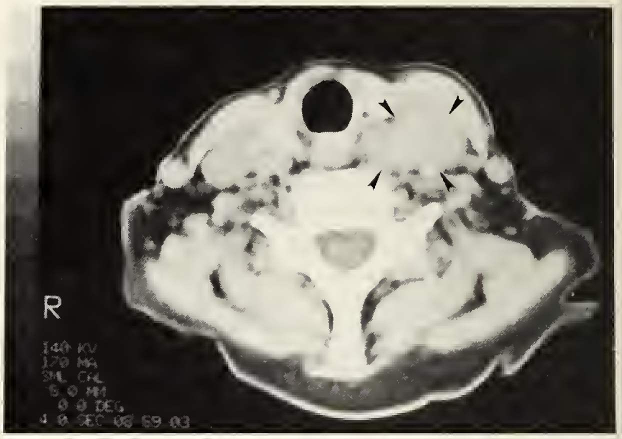

Figure 1. *Computed tomogram of neck in patient 1 showing mass (arrows), displacing carotid artery anteriorly, and contiguous with thyroid gland.*

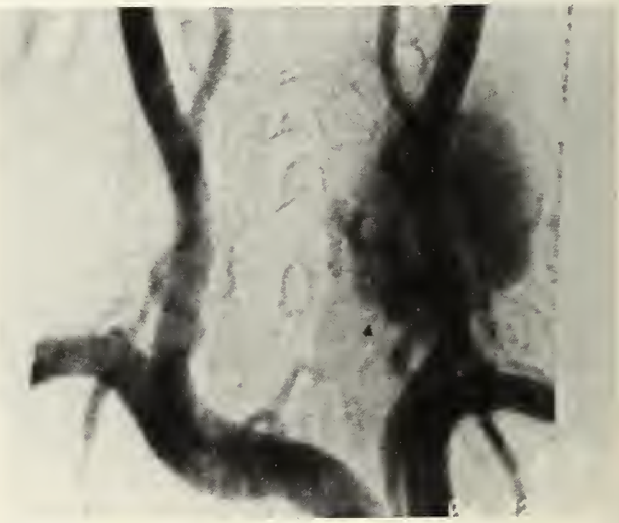

Figure 2. *Arch arteriogram demonstrating highly vascular mass supplied by the thyroidal artery.*

From 306 S. Gregson Street, Durham 27701 and Department of Medicine, Duke University Medical Center, Durham 27710.

At neck exploration the mass was removed from between the longus colli muscle posteriorly and the carotid anteriorly. It was adherent to, but did not emanate from, either the carotid artery or the vagus nerve but arose from the middle sympathetic cervical ganglion. Histological study revealed a paraganglioma. Postoperatively she did well except for the development of a mild Horner's syndrome on the left due to removal of the diseased middle cervical ganglion.

Comment

This and the following case studies illustrate several features concerning diagnostic strategy for an adult over age 35 who presents with a single neck mass. We make several assumptions at the outset:

1. a neck mass in an adult is considered malignant until proven otherwise;
2. tissue is needed to prove or disprove malignancy;
3. chances for cure diminish if surgical violation of cervical fascial planes occurs without removing all malignant tissue;
4. primary neoplasms may be occult and must be searched for;
5. the nature and location of the tumor and/or metastases determine prognosis.

All successful strategies begin with a thorough history and physical examination which are said to reveal the most likely diagnosis ninety percent of the time.[1] Knowledge of the epidemiology of neck masses as well as the detailed anatomy of the neck is essential. Ultrasonography and radiographic imaging are important, but should be tailored to the findings on history and physical examination. Our patient had a lump in the anterior triangle of the neck where diagnostic possibilities include developmental anomalies (lateral cervical, dermoid, epidermoid, and thymus cysts), infection (lymphadenitis, mononucleosis, and granulomatous diseases), or neoplasms (primary or metastatic, benign or malignant). Reports from tertiary care centers claim that more than eighty percent of neck lumps in patients over age 40 are neoplastic.[2] However, one "general" otolaryngology clinic in Norway reported 48% infectious, 38% neoplastic (16% malignant), and 14% other categories.[3] Cervical adenitis, either acute (streptococcus, staphylococcus, mononucleosis, cat stratch fever) or subacute (cat scratch fever, toxoplasmosis, cytomegalovirus, psittacosis or tuberculosis), is more common in children. Of the congenital anomalies, dermoid cysts are more common in children but thyroglossal duct cysts and some branchial cleft cysts are common in adults. Most malignant masses are metastatic in origin, usually from squamous cell carcinoma of the head and neck. Cancer is more likely in the presence of certain risk factors: smoking (incidence of cancer increases steeply after 20 pack-year history); alcohol intake; prior neck irradiation; history of other tumors; exposure to asbestos, woodworking (which increases chances of nasopharyngeal and paranasal sinus tumors), and leather tanning processes (secondary to chromic acid exposure). Our patient had none of these risk factors.

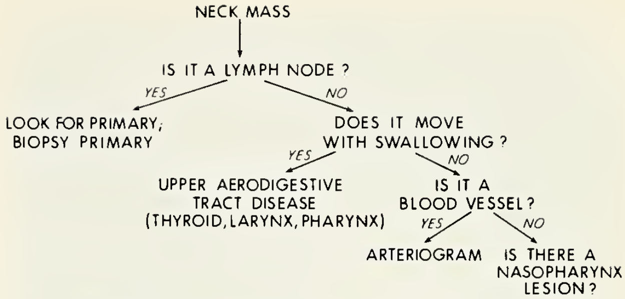
NECK MASS
IS IT A LYMPH NODE ?
YES
NO
LOOK FOR PRIMARY; BIOPSY PRIMARY
DOES IT MOVE WITH SWALLOWING ?
YES
NO
UPPER AERODIGESTIVE TRACT DISEASE (THYROID, LARYNX, PHARYNX)
IS IT A BLOOD VESSEL ?
YES
NO
ARTERIOGRAM
IS THERE A NASOPHARYNX LESION ?

Figure 3. *Algorithm for evaluation of a neck mass.*

Physical examination of the neck can answer several questions (figure 3). The first is whether or not the mass is a lymph node. Location of the mass and feel are important here. Most neck nodes lie in two major anatomical areas referred to as the anterior and posterior triangles (figure 4). The distribution of lymph nodes in the anterior triangle resembles a tilted T extending from the tragus to the sternal notch, anterior to the sternocleidomastoid and along the lower edge of the mandible. The distribution of nodes in the posterior triangle, below the sternocleidomastoid, is L-shaped and follows the spinal accessory nerve and the external jugular vein.

Remember to seat the patient in a chair and stand behind to examine nodes in the neck. Look for consistency, size, tenderness, fluctuance, and whether they are single or matted. The salivary and parotid glands can be confused with lymph nodes, especially in elderly patients. These can be ptotic and palpable without being diseased. Bimanual palpation with one finger in the patient's mouth and another external over the area of the submandibular gland can often delineate gland anatomy. The parotid can sometimes be defined better with forward traction on preauricular skin.

If the lump is a node, the area it drains must be examined to locate a primary source. Nodes in the anterior triangle subserve the anterior third of the scalp as well as facial structures, oral cavity, pharynx, thyroid, salivary gland and sinus cavities. Nodes in the posterior triangle drain the posterior two-thirds of the scalp and nasopharynx. In general, nodes in the upper parts of the neck arise from head

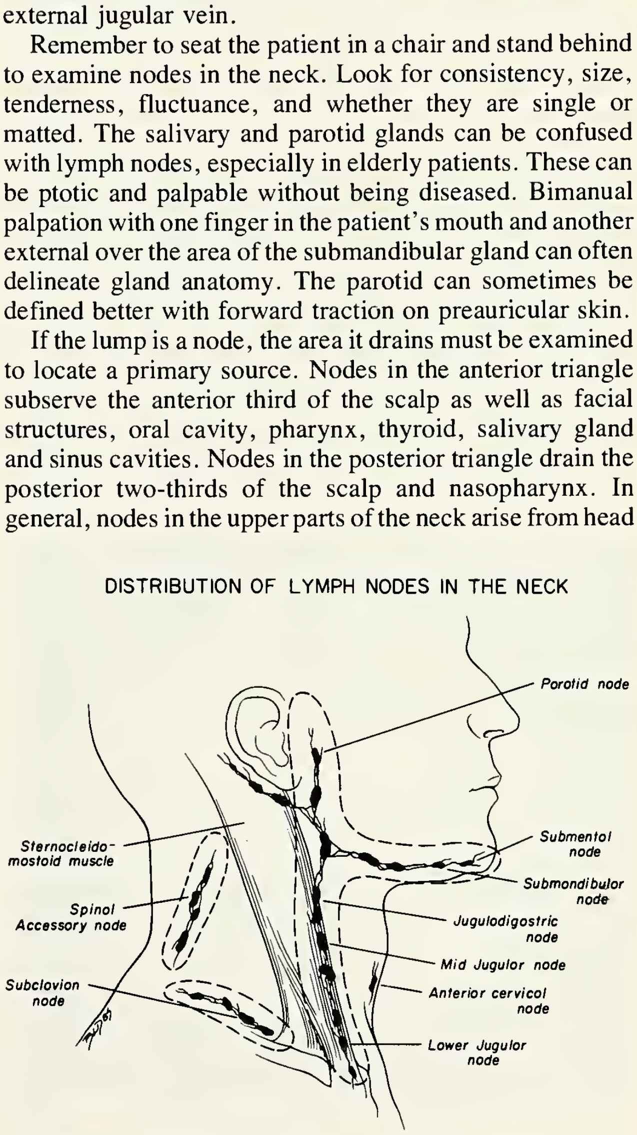

Figure 4. *Distribution of lymph nodes in the neck.*

and neck primaries while lower neck nodes arise from an infraclavicular site. A left supraclavicular node ("Virchow's node") raises the question of an abdominal primary. Midline or paratracheal sites suggest larynx, thyroid, or pulmonary sites. Bilateral nodes can mean lymphoma or a supraglottic, base of tongue, or anterior oral cavity primary since these structures have bilateral lymph drainage. In our patient the mass appeared to be beneath the sternocleidomastoid and did not feel like a node.

A second important observation is whether or not the mass moves with swallowing. Structures belonging to, or attached to, the upper aerodigestive tract move up and down with swallowing. The upper aerodigestive tract is the funnel-shaped group of organs (pharynx, larynx, trachea, and thyroid) suspended from the hyoid bone. The only nodes in this tract are the delphian nodes in the thyrohyoid membrane, which can be enlarged with thyroid or laryngeal cancer. Since the mass in our patient did not move with swallowing, we concluded that it was not part of the aerodigestive tract.

Next one must decide whether the mass is of blood vessel origin. These are peripheral to the visceral funnel, are usually pulsatile, occasionally are associated with a bruit, and can usually be moved side to side, but not up and down because they are attached to the carotid sheath. Carotid body tumors and chemodectomas occur frequently at the bifurcation of the common carotid. The lump in our patient had displaced the left carotid anteriorly but the artery itself did not appear to be enlarged and contained no bruit. Although it appeared intimately involved with the carotid artery, it could be moved side to side and up and down.

The nasopharynx and base of the tongue must also be examined. Tumors of the tongue can be submucosal and be missed by visual inspection, even with mirrors. Some of these can be felt with a digital examination. If a node contains metastatic cancer for which no primary source is found, blind biopsy of the base of the tongue may be indicated.

At the end of the history and physical, we were certain only that our patient had a mass beneath the left sternocleidomastoid muscle in the middle third of the neck. It seemed close to but distinct from the thyroid gland and close to but distinct from the carotid artery. Because of the uncertainty, x-ray and laboratory tests were performed.

Thyroid scan did not demonstrate the mass. There was decreased uptake in the left lower pole but it wasn't certain that this was due to the lump in question as no mass could be felt in the thyroid.

Ultrasonography was considered but omitted because the mass lay deep in the neck and ultrasonography works better for lesions closer to the surface.[5] Computed tomographic (CT) scan can define the extent of soft tissue involvement and altered anatomical relationships in many patients with neck masses; when used with contrast it can define relationships to the major vessels.[6] In this case, although the extent was well defined by CT scan, the origin of the mass could not be clearly defined, especially whether or not it arose from the throid gland. It did appear vascular and an arteriogram confirmed this. Its blood supply came from the left inferior and superior thyroidal arteries but on physical examination it felt clearly distinct from the thyroid. Since it did not appear to be a metastatic node, but rather a primary tumor, the next step was an excisional biopsy which revealed a benign paraganglioma.

Case 2

A 75-year-old woman came to the medical clinic complaining of severe cough, especially when supine, and difficulty swallowing solids and liquids. She had some pain in her throat, hoarseness, weight loss, and a fullness in her neck but no fever, chills, abdominal pain, nausea, vomiting, diarrhea, constipation, or skin changes. On physical examination she was anxious and chronically ill-appearing. Vital signs were normal except for tachypnea (24 breaths per minute). Head, eyes, nose, and throat were normal. Neck examination revealed a fullness in the area of the thyroid. The thyroid was easily palpable, firm, nonnodular, and minimally enlarged. The thyroid and larynx were pushed forward. Her voice was hoarse. Lung examination revealed stridorous breathing and a brassy cough, especially when recumbent. High pitched wheezing primarily on inspiration but also on expiration was heard over the larynx, but the lungs were clear. The remainder of the examination was normal.

Comments

Table 1 lists clues derived from a patient history that can help to localize the probable site of a neck mass and its nature. Careful questioning is imperative but not always easy. Patients may not always formulate their complaint with precision and physicians may not always critically evaluate the complaint. When questioned carefully, our patient demonstrated several of the classic symptoms of head and neck disease. She complained of difficulty swallowing both solid and liquid meals but not saliva between meals. This latter point helps to differentiate true dysphagia from globus hystericus or postnasal drip which can cause a vague sensation of difficult swallowing but tends to occur between meals. Of course, with nearly complete obstruction of the esophagus the patient can have difficulty swallowing even oral secretions. Our patient localized her site of obstruction to the back of her throat rather than the lower

Table 1
Neck Masses:
Useful Clues from the History

Risk Factors Associated with Increased Risk of Cancer	Increasing Age Sex — males more likely to develop lip cancer Race — whites more likely to develop lip cancer Exposure — alcohol, wood working, tanning, asbestos, x-ray, sun. Tobacco — smoking, dipping.
Historical Features That Localize Lesion	Dysphagia Odynophagia Referred pain Hoarseness Respiratory Stridor Cough

esophagus or stomach. Patients can often localize well the area of disease when the site is above the upper esophageal sphincter but not as well when below. She had some weight loss, ate slowly, and tended to choke on her food which supported the interpretation of true dysphagia. Painful swallowing (odynophagia) also helps to distinguish local structural disease from globus hystericus. It suggests conditions such as lingual tonsillitis or neoplasms of pharynx, larynx, oral cavity, or tongue. Because of the distribution of cranial nerves V, IX, and X, painful swallowing can be felt in the ear, but our patient did not have this problem.

Hoarseness with a mass in the neck strongly suggests cancer (causing vocal cord or recurrent laryngeal nerve dysfunction). Inspiratory stridor, diagnostic of upper airway obstruction, is produced when a soft tissue obstruction collapses into the airway on inspiration and vibrates. In expiration the positive air pressure forces soft tissues apart and decreases the vibration. Lower airway obstructions behave oppositely in that on inspiration the airways open, while on expiration they tend to collapse leading to increased vibration and stridor. Tracheal stridor tends to be present on both inspiration and expiration. Our patient had inspiratory stridor placing the lesion in the laryngeal area. The symptoms strongly suggested cancer.

Indirect laryngoscopy revealed a paralyzed vocal cord, but no mass, thus implicating recurrent laryngeal nerve pressure. Soft tissue lateral x-ray of the neck confirmed the presence of a mass in the area of the thyroid, behind the trachea (figure 5). Barium swallow showed a marked extrinsic obstruction of the upper esophagus (figure 6). Chest x-ray was normal. Thyroid scan showed no uptake in the left lobe, suggesting that the mass might be of thyroid origin. While the evaluation was in progress, the patient had a cardiac arrest and died. Autopsy showed anaplastic carcinoma of the thyroid with metastases to bone and liver, skull, and lymph nodes.

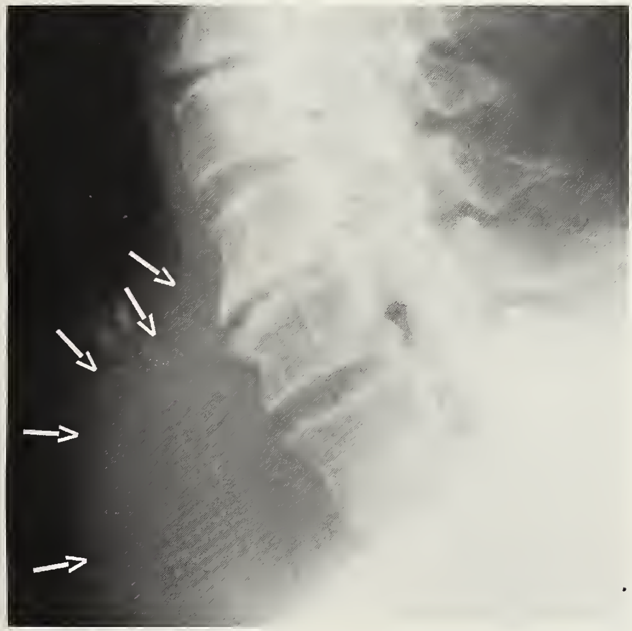

Figure 5. *Soft tissue x-ray of neck demonstrating mass (arrows).*

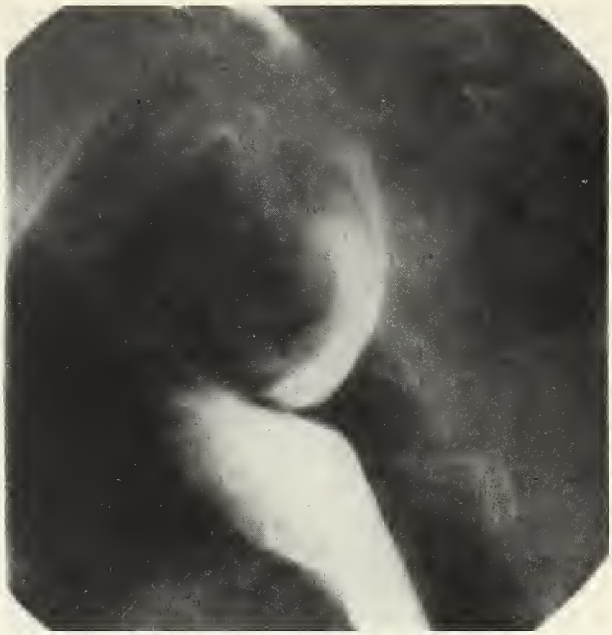

Figure 6. *Barium swallow of patient 2 demonstrates near obstruction of esophagus at level of thyroid.*

Case 3

A 35-year-old woman was noted by friends to have a slightly asymmetrical neck. She then noted a slight, painless swelling below the left sternocleidomastoid muscle. She had no symptoms. She had been treated with I^{131} for hyperthyroidism several years previously and now took standard doses of thyroxine to maintain euthyroidism.

On physical examination the left sternocleidomastoid was more prominent than the right. No definite margins could be palpated and there was no discoloration, ecchymoses, or erythema. No thyroid tissue could be felt. Ultrasonography of the neck showed a cystic mass, compatible

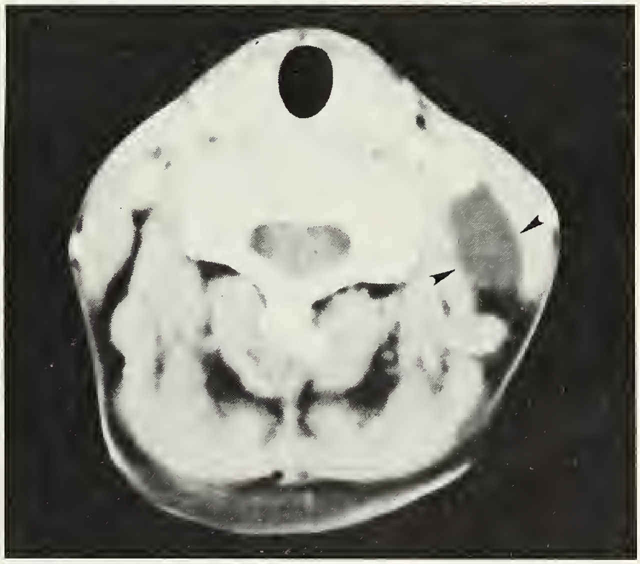

Figure 7. *Computed tomogram of neck in patient 3 demonstrating cystic mass (arrows) in posterior triangle.*

with a branchial cleft cyst or possibly with a dilated jugular venous structure.

Comment

In distinction to our other two patients, neither history or physical examination gave specific clues as to the etiology of the prominent sternocleidomastoid in this patient. The lack of symptoms and findings suggested a benign process, such as thyroglossal duct cyst, branchial cleft cyst, sialolithiasis, sialadenitis, cervical adenopathy, chemodectoma, laryngocoele or pharyngocoele.

CT scan of the neck (figure 7) showed a cystic structure beneath the sternocleidomastoid which appeared to be a cystic hygroma. This was removed surgically; the pathologist confirmed the diagnosis of a cystic hygroma. The patient has done well since.

Summary

Primary care physicians see most adult patients with a lump in the neck. Knowledge of the epidemiology of neck masses, the anatomy of the neck, the appropriate use of history and physical examination, and the capabilities of imaging techniques is essential to choosing appropriate diagnostic strategies for these patients.

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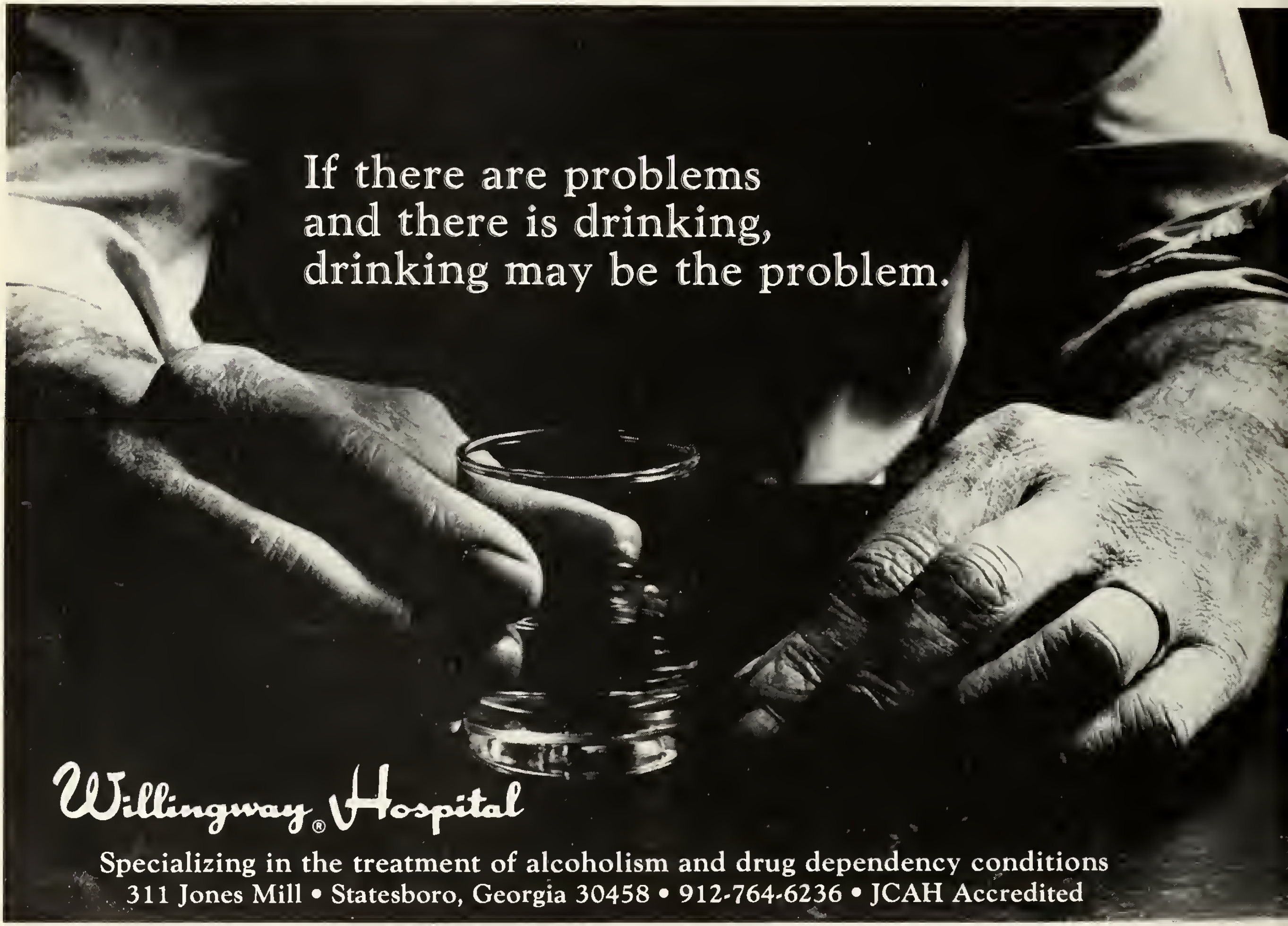
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Statewide Prehospital Mobile Intensive Care Treatment Protocols for Advanced Life Support Units in North Carolina

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Introduction

The EMSS Acts of 1973 and 1976 mandated the development and implementation of prehospital care protocols as guidelines for optimal patient care under direct medical supervision. When direct radio control cannot be or has not been established, further step-by-step guidelines, or standing orders, are necessary. This document presents a selected set of guidelines, or protocols which, at the discretion of individual medical directors, may be used as standing orders. The development of uniform, specific protocols is desirable as a mechanism for standardizing emergency treatment throughout a region or state. Standardization of emergency treatment will aid in providing optimal patient care. They also provide a starting point for quality assurance and medical control. They aid in the development of a rational approach to training and monitoring performance of EMS personnel, as well as providing medicolegal protection for their activities. Finally, they simplify the EMS personnel's task of transporting a moderately to seriously ill patient over distances that may encompass more than one regional area of medical control.

The protocols for both adult and pediatric patients contained herein are those pertaining to Advanced Life Support field care only. With standardized training, equipment, drugs, etc., this would lend itself well to uniformity of care and review. Where feasible they are presented in both outline and algorithm form for maximum flow of patient care. It is expected that each of these will be subject to clinical study, and validated or revised through a continuous monitoring process, thus assuring quality of care. The need for additional protocols should be identified through this same evaluation process and developed accordingly.

These protocols have been extensively reviewed and revised after significant contributions by medical control physicians throughout this state as well as South Carolina and the District of Columbia. It is hoped that they will serve as a basis for prehospital critical care within the boundaries of mature medical judgment.

(Because of the considerable length of these protocols, additional funding for publication costs was provided by the North Carolina Chapter of the American College of Emergency Physicians and the Department of Emergency Medicine at East Carolina University School of Medicine.)

From the *Departments of Emergency Medicine, East Carolina University School of Medicine, †Bowman Gray School of Medicine and ‡Charlotte Memorial Hospital.

Prehospital Critical Care Treatment Protocols

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Prehospital Treatment of Cardiac Arrest (Adult)

A. **Definition** — Cardiac arrest is the cessation of effective cardiac contraction. The two most common causes are: (1) cardiac standstill or asystole and (2) ventricular fibrillation. A less common cause is *electromechanical dissociation* (cardiovascular collapse). Rarely, *ventricular tachycardia* can cause cardiac arrest.

B. **Etiology** — Conditions commonly associated with cardiac arrest are:

(1) Acute myocardial infarction
(2) Heart blocks
(3) Valvular heart disease (IHSS, etc.)
*(4) Pericardial tamponade
(5) Acute pulmonary embolism
*(6) Tension pneumothorax
(7) Cerebrovascular disease
(8) Drugs present in toxic levels (potassium, digitalis, etc.)
*(9) Excessive loss of blood volume

C. **Diagnosis** — Time should not be wasted in making the diagnosis as irreversible brain damage may occur in 3-4 minutes. If the following signs are present, immediate treatment per protocol should be started:

---

* In the setting of severe trauma cardiac arrest is handled differently than that due to non-traumatic causes. In trauma the time factor is a major determinant of mortality and morbidity, and transport and stabilization should be handled simultaneously.

(1) Unconsciousness that does not immediately respond with assumption of the supine position.
(2) Absent or gasping respirations.
(3) Absent pulsations in a major artery (carotid, brachial, or femoral).

Confirmation of the arrest state by electrocardiographic evidence of asystole or ventricular fibrillation is not necessary at this time.

Treatment Protocol A-0 (Cardiac Arrest, Adult)

1. Recognize cardiac arrest: unresponsive, apneic, pulseless.
2. Open the airway.
3. Assist ventilation:
   A. Mouth-to-mouth or
   B. Bag/mask with supplemental O_2 at 8-15 L/min with reservoir.
4. Perform the appropriate maneuvers if airway obstruction is suspected. (Protocol A-2)
5. Begin external cardiac compression with the patient supine on a firm surface.
6. Monitor cardiac activity: make sure all lead connections intact
   A. If *ventricular fibrillation* begin Protocol A-0-1.
   B. If *asystole* begin Protocol A-0-2.
   C. If *electromechanical dissociation* begin Protocol A-0-3.
   D. If *ventricular tachycardia* begin Protocol B-0-1.

Treatment Protocol A-0-1 (Ventricular Fibrillation)[a]

Make sure all lead connections intact.

1. Defibrillate (200-300 watt-seconds).[b]
2. If no response, recharge and defibrillate again.
3. Intubate (E-T or EOA) if necessary.
4. Place IV line. Infuse D_5W at KVO rate.
5. Give:
   A. Sodium bicarbonate (1 mEq/kg) IV push and
   B. Epinephrine (5-10 cc of 1:10,000) IV push or endotracheally.
6. Defibrillate (360-400 watt-seconds). If no response immediately, defibrillate again.
7. Give either:
   A. Bretylium (350-500 mg or 5 mg/kg) IV push
   OR
   B. Lidocaine (1 mg/kg) IV push followed by Lidocaine infusion (1 g in 250 cc D_5W = 4 mg/cc) at 0.5-1 cc/min.
8. Defibrillate again after two minutes.
9. Give either:
   A. Bretylium (350-500 mg or 5 mg/kg) IV push
   OR
   B. Lidocaine (0.5 mg/kg) IV push.
10. Give sodium bicarbonate (0.5 mEq/kg) IV push if 10 minutes have elapsed since last dose.
11. Defibrillate again.
12. Give:
   A. Epinephrine (5-10 cc of 1:10,000) IV push or endotracheally every five minutes and
   B. Sodium bicarbonate (0.5 mEq/kg) IV push every 10 minutes and
   C. Bretylium (10 mg/kg) IV push every 15 minutes OR Lidocaine (0.5 mg/kg) IV push every 5-10 minutes.
13. Continue CPR and the drug regimen in step 12 until transport is completed.[c]

---

[a] Although not specifically stated in the protocol, CPR should be continued throughout the protocol sequence without interruption except during defibrillations.

[b] If at any time during the resuscitation the patient reverts to normal rhythm, Protocol A-0-4 should be followed.

[c] Loading and transport should not interfere with the sequence outlined in the protocol. If it seems that they will interfere, the unit should remain on the scene at least through step 11.

Treatment Protocol A-0-2 (Asystole)[a]

Make sure all lead connections intact for recording device.

1. Intubate (E-T or EOA) if necessary.
2. Place IV line. Infuse D_5W at KVO rate.[b]
3. Give:
   A. Sodium bicarbonate (1 mEq/kg) IV push and
   B. Epinephrine (5-10 cc of 1:10,000) IV push or endotracheally.
   (Repeat B at five-minute intervals as needed and A at one-half the original dose at 10 minute intervals as needed.)
4. Give atropine (1.0 mg) IV push. Repeat once if there is no immediate response.
5. Give calcium chloride (5 cc of 10 percent solution) slow IV push. Repeat at 10 minute intervals as needed.[c]
6. Repeat steps 3 and 5 as needed. If there still is no response after second dose of calcium chloride begin an isoproterenol infusion.[d]
7. Defibrillate 360-400 ws. May repeat × 1.
8. Continue CPR and the drug regimen in step 6 until transport is completed.

---

[a] CPR should be continued throughout the protocol sequence without interruption.

[b] If at any time during the resuscitation the patient reverts to normal rhythm, Protocol A-0-5 should be followed.

[c] The role of calcium in resuscitation is controversial. Experimental studies have shown an accumulation of calcium ions in the hypoxic myocardium with subsequent uncoupling of mitochondrial oxidative phosphorylation. At the present time, however, calcium is still considered clinically indicated. (Nayler WG et al. Cardiovascular receptors and calcium. Circ Res 1980;46:1161.) See the collected research of Blaine White et al on calcium and resuscitation.

[d] Isoproterenol (1 mg in 250 cc D_5W = 4 mcg/cc) at infusion rate of 1-5 cc/min.

Treatment Protocol A-0-3 (Electromechanical Dissociation)[a]

Make sure all lead connections intact.

1. Intubate (E-T or EOA) if necessary.
2. Place IV line. Infuse D_5W at KVO rate.[b, c]

3. Give:
   A. Sodium bicarbonate (1 mEq/kg) IV push and
   B. Epinephrine (5-10 cc of 1:10,000) IV push or endotracheally.
   (Repeat B at five-minute intervals as needed and A at one-half the original dose at 10-minute intervals as needed.)
4. Give calcium chloride (5 cc of 10 percent solution) slow IV push. Repeat at 10-minute intervals as needed.[d]
5. Repeat steps 3 and 4 above as needed.
6. Begin isoproterenol infusion (1 mg in 250 cc D_5W = 4 mcg/cc) at rate of 0.5-5 cc/min.
7. Continue CPR and the drug regimens in steps 5 and 6 until transport is completed.[e]

---

[a] Electromechanical dissociation is often secondary to hypovolemia, cardiac tamponade or rupture, or tension pneumothorax. *Volume replacement* may be an important part of therapy. Pleural decompression should be performed in suspected tension pneumothorax.

[b] CPR should be continued throughout the protocol sequence without interruption.

[c] If at any time during the resuscitation the patient reverts to normal hemodynamic parameters, Protocol A-0-5 should be followed.

[d] See footnote c., Protocol A-0-2.

[e] Loading and transport should not interfere with the sequence outlined in the protocol. If it seems that they will interfere, the unit should contact Medical Control to determine the number of steps taken. Electromechanical dissociation secondary to trauma is an exception; transport and treatment should be attempted simultaneously.

Treatment Protocol A-0-4
(Following Termination of Ventricular Fibrillation)

1. Stop at the appropriate step in Protocol A-0-1 if ventricular fibrillation has been terminated.
2. Start IV if not already in place. Infuse D_5W at KVO rate.
3. Give:
   A. Lidocaine (1 mg/kg) IV push and follow with
   B. Lidocaine infusion (1 g in 250 cc D_5W = 4 mg/cc) at 0.5-1 cc/min.
   C. Follow the Lidocaine infusion with a second bolus of Lidocaine (0.5 mg/kg) IV push after five minutes
   OR
   A. Bretylium (350-500 mg or 5 mg/kg) IV push and follow with
   B. Bretylium infusion (500 mg in 250 cc D_5W = 2 mg/cc) at 0.5-1 cc/min.[a]
4. Continue steps 2 and 3 until transport is completed.

---

[a] Until further convincing research to the contrary appears, Lidocaine is still preferred over Bretylium as the drug of first choice.

Treatment Protocol A-0-5
(Following Termination of Asystole or Electromechanical Dissociation)

1. Stop at the appropriate step in Protocol A-0-2 or A-0-3 if asystole or electromechanical dissociation has been terminated.
2. Continue IV of D_5W at KVO rate.
3. Initiate additional therapy for:
   A. Hypotension (systolic <90) — use Protocol A-0-6.
   B. Bradycardia (rate <50) — use Protocol A-0-7.
   C. PVCs — use Protocol A-0-4.
4. Resume Protocol A-0-2 or A-0-3 if asystole or electromechanical dissociation recurs.
5. Continue these steps until transport is completed.

Treatment Protocol A-0-6
(Hypotension [Systolic <90] Following Termination of Asystole, Ventricular Fibrillation, or Electromechanical Dissociation or Suspected MI with Bradycardia)

1. Assess volume status (pulse, BP, evidence of blood loss, etc.). If hypovolemia is suspected, begin trial of volume infusion with Ringer's lactate 100-200 cc boluses at 5-10 minute intervals.
2. Give atropine (0.5 mg) IV push every five minutes (to 2.0 mg) if the hypotension is associated with bradycardia (rate <60).
3. Begin Dopamine infusion if there is no evidence of hypovolemia or if volume infusion fails and if no bradycardia exists.[a]
4. Continue these steps until transport is completed.

---

[a] Dopamine infusion (200 mg in 250 cc D_5W = 800 mcg/cc). Begin at 0.5 cc/min and titrate.

Treatment Protocol A-0-7
(Bradycardia [rate <50] Following Termination of Asystole, Ventricular Fibrillation, or Electromechanical Dissociation or Suspected MI with Bradycardia and Hypotension)

1. Give atropine (0.5 mg) IV push every five minutes (2.0 mg total dose) until the heart rate is >60.
2. Reassess heart rate and blood pressure:
   A. Begin Protocol A-0-6 if rate increases to >60 but systolic pressure is <90 or
   B. Observe the patient if rate increases to >60 and systolic pressure is >90.
3. Begin Isoproterenol infusion (1 mg in 250 cc D_5W = 4 mcg/cc) at rate of 1-5 cc/min if rate fails to increase after steps 1 and 2.[a]
4. Continue these steps until transport is completed.

---

[a] If the Isoproterenol infusion fails to accelerate the heart rate, a pacemaker is the only therapy possible.

Treatment Protocol A-2

Prehospital Treatment of Respiratory Arrest

A. **Definition** — Respiratory arrest may be defined as the cessation of breathing. Primary respiratory arrest may lead to cardiac arrest within minutes if the ensuing hypoxia persists. Primary cardiac arrest leads to respiratory arrest but in a shorter period of time. As noted in Protocol A-1, primary respiratory arrest is the most common cause of cardiac arrest in infants and children.

B. **Etiology** — In adults the conditions most often associated with respiratory arrest are:
   1. Acute airway obstruction
   2. Aspiration
   3. Acute hypoxia
   4. Stroke
   5. Overdose of sedatives, hypnotics, narcotics
   6. Hypothermia
   7. Electrical shock
   8. Drowning or near-drowning

   The conditions most commonly associated with respiratory (cardiac) arrest in children and infants are given in Protocol A-1.

C. **Diagnosis** — Pertinent history may or may not be attainable. Airway management/breathing should not be delayed as time is crucial. If any of the following signs are present, the protocol should be immediately implemented.
   1. Absent or gasping respiration.
   2. Unconsciousness associated with absent or labored respiration.
   3. Cyanosis and absent or gasping respiration.

Treatment Protocol A-2
(Respiratory Arrest)

1. Recognize respiratory arrest: apneic or gasping respiration, unconscious.
2. Open the airway.
3. Assist ventilation:
   A. Mouth-to-mouth or mouth-to-mask with supplemental oxygen
   B. Bag/mask with supplemental O_2 at 8-15 L/min. with reservoir
4. If unable to ventilate consider obstruction and do the following in sequence:
   A. Apply four back blows rapidly.
   B. Apply four manual abdominal thrusts.
   C. Apply the finger sweep.
   D. Directly visualize the upper airway and remove obstruction.

   (If still unable to ventilate continue steps 2, 3, and 4, transport and continue with the remainder of the protocol.)
5. Check peripheral pulse (carotid). If absent, proceed with cardiac arrest protocols (A-0, A-0-1, A-0-2, A-0-3 or A-1). If present continue with the remainder of the protocol.
6. Intubate (E-T or EOA) if necessary.
7. Place IV line. Infuse D_5W at KVO rate.
8. Monitor cardiac activity.
9. Continue airway maintenance and ventilation assistance if necessary until transport is complete.

The Medical Control physician may want to give Na bicarbonate 1 mEq/kg IV.

Treatment Protocols
B-0, B-0-1, B-0-2, B-0-3

Prehospital Treatment of Acute Myocardial Infarction

A. **Definition** — Myocardial infarction is necrosis of a variable amount of heart muscle due to inadequate blood supply. This is usually due to coronary atherosclerosis with or without thrombosis. Spasm of coronary vessels plays a significant role in some patients.

B. **Etiology** — Myocardial infarction kills because of *dysrhythmia* (early complication) or *pump failure* (later complication). The prehospital treatment of acute myocardial infarction is directed primarily toward the following:
   1. Provision of supplemental O_2.
   2. Management of selected dysrhythmias.
   3. Management of shock and/or pulmonary edema.
   4. Relief of pain/anxiety.
   5. *Rapid transport.*

C. **Diagnosis** — The history may be classic (substernal, prolonged chest pain with radiation into the neck and left arm, dyspnea, anxiety, etc.) or more subtle (poorly described chest pain, fatigue). On examination the patient may be anxious, diaphoretic, nauseated and/or hypotensive. The pulse may be rapid, slow, or irregular. There may be rales or wheezes on auscultation of the lungs. The diagnosis requires knowledge of other conditions which can cause acute, prolonged chest pain. The most important of these are:
   1. Dissecting aortic aneurysm.
   2. Pulmonary embolism.
   3. Spontaneous pneumothorax.

Treatment Protocol B-0
(Acute Myocardial Infarction)

1. Recognize acute myocardial infarction: acute, prolonged chest pain, etc.
2. Administer O_2 by mask or nasal prongs at 6 L/min.
3. Place patient in a position of comfort (usually this is sitting at a 45° angle).
4. Place IV line. Infuse D_5W at KVO rate.
5. Monitor cardiac activity and call Medical Control.
6. If BP >100 systolic, NTG 1/150 gr sublingually — observe for relief of pain — may repeat × 2 q 5 min.
7. If available, give morphine sulfate (2-4 mg) IV slowly (1 min) every five to 15 minutes as necessary to relieve pain and anxiety.[a]
8. Give:
   A. Lidocaine (1 mg/kg) IV push and follow with
   B. Lidocaine infusion (1 g in 250 cc D_5W = 4 mg/cc) at 0.5-1 cc/min.
   C. Follow the Lidocaine infusion with a second bolus of Lidocaine (0.5 mg/kg) IV push after five minutes.[b]
9. Treat the following dysrhythmias:
   A. Ventricular fibrillation/tachycardia — use Protocols A-0-1 and B-0-1.
   B. Bradycardia (rate <50) — use Protocol A-0-7.
   C. Bradycardia (rate <60) and hypotension — use Protocol A-0-6.
   D. PVCs — step 8 above.

10. Treat pulmonary edema — use Protocol B-0-2.
11. Treat hypotension and shock — use Protocol B-0-3.
12. Treat supraventricular tachycardia — use Protocol B-0-4.
13. Complete heart block or Mobitz Type II — use Protocol B-0-5.
14. Continue these steps until transport is completed.

---

[a] Morphine sulfate reduces preload by increasing systemic venous capacitance. This helps to relieve pulmonary vascular congestion (edema). The reduced preload may lead to a decrease in cardiac output and a subsequent drop in blood pressure. *Vital signs* must therefore be monitored frequently.

[b] Many studies have shown that the early use of IV Lidocaine can significantly reduce the incidence of primary ventricular fibrillation even in the absence of warning dysrhythmias. Its prophylactic use should be left to the discretion of the local Medical Director.

Treatment Protocol B-0-1
(Ventricular Tachycardia)

1. If onset of dysrhythmia is witnessed, administer a chest "thump."
2. Proceed in the following manner for the appropriate clinical situation:

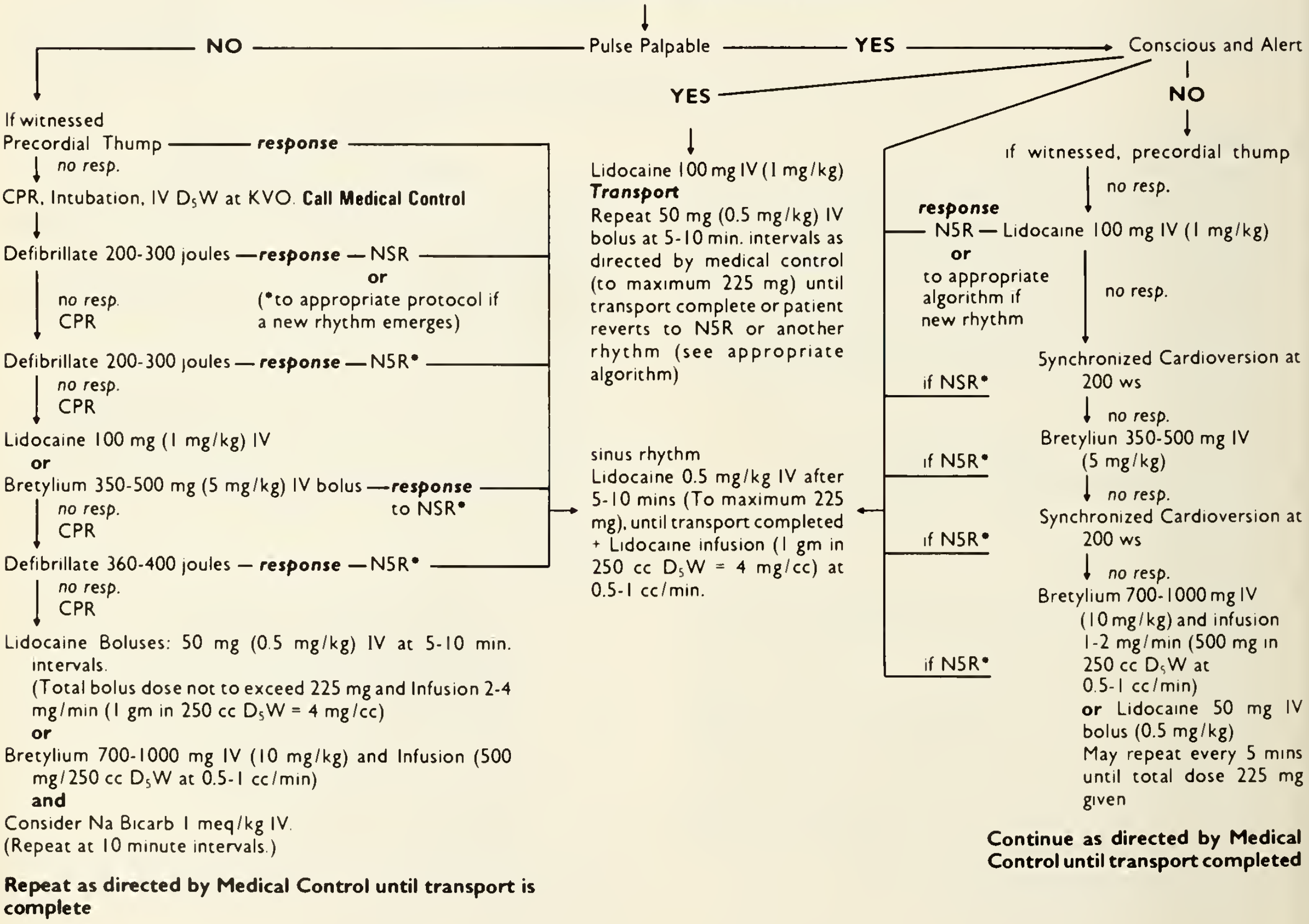
No pulse by monitor, with leads checked, *unconscious*

A. Begin CPR, Intubate, IV D5W KVO. Call Medical Control.
B. Defibrillate 200-300 joules
Check pulse — change in rhythm → appropriate protocol. No change, continue CPR.
C. Recharge — Defibrillate 200-300 joules
Check pulse — change in rhythm → appropriate protocol. No change, continue CPR.
D. Lidocaine 100 mg (1 mg/kg) IV
or
Bretylium 350-500 mg (5 mg/kg) IV bolus
E. Defibrillate 360-400 joules
Check pulse — change in rhythm → appropriate protocol. No change, continue CPR.
F. Bretylium 700-1000 mg IV (10 mg/kg) bolus and infusion 500 mg/250 cc D5W at 0.5-1 cc/min
or
Lidocaine boluses 50 mg (0.5 mg/kg) at 5-10 min intervals, total dose not to exceed 225 mg and infusion 2-4 mg/min
G. Consider NaBicarb 1 mEq/kg IV. Repeat q 10 min as directed by Medical Control until completed.

Pulse present, conscious

A. Lidocaine 100 mg (1 mg/kg) IV
B. Transport
C. Repeat 50-75 mg boluses every 5-10 minutes to maximum of 225 mg.

VENTRICULAR TACHYCARDIA


Pulse Palpable
NO
YES
Conscious and Alert
If witnessed Precordial Thump
response
no resp.
CPR, Intubation, IV D₅W at KVO. Call Medical Control
Defibrillate 200-300 joules — response — NSR
or
(*to appropriate protocol if a new rhythm emerges)
no resp. CPR
Defibrillate 200-300 joules — response — NSR*
no resp. CPR
Lidocaine 100 mg (1 mg/kg) IV
or
Bretylium 350-500 mg (5 mg/kg) IV bolus — response to NSR*
no resp. CPR
Defibrillate 360-400 joules — response — NSR*
no resp. CPR
Lidocaine Boluses: 50 mg (0.5 mg/kg) IV at 5-10 min. intervals. (Total bolus dose not to exceed 225 mg and Infusion 2-4 mg/min (1 gm in 250 cc D₅W = 4 mg/cc)
or
Bretylium 700-1000 mg IV (10 mg/kg) and Infusion (500 mg/250 cc D₅W at 0.5-1 cc/min)
and
Consider Na Bicarb 1 meq/kg IV. (Repeat at 10 minute intervals.)
Repeat as directed by Medical Control until transport is complete
YES
Lidocaine 100 mg IV (1 mg/kg)
Transport
Repeat 50 mg (0.5 mg/kg) IV bolus at 5-10 min. intervals as directed by medical control (to maximum 225 mg) until transport complete or patient reverts to NSR or another rhythm (see appropriate algorithm)
sinus rhythm
Lidocaine 0.5 mg/kg IV after 5-10 mins (To maximum 225 mg), until transport completed + Lidocaine infusion (1 gm in 250 cc D₅W = 4 mg/cc) at 0.5-1 cc/min.
NO
if witnessed, precordial thump
no resp.
response
NSR — Lidocaine 100 mg IV (1 mg/kg)
or
to appropriate algorithm if new rhythm
no resp.
Synchronized Cardioversion at 200 ws
if NSR*
no resp.
Bretyliun 350-500 mg IV (5 mg/kg)
if NSR*
no resp.
Synchronized Cardioversion at 200 ws
if NSR*
no resp.
Bretylium 700-1000 mg IV (10 mg/kg) and infusion 1-2 mg/min (500 mg in 250 cc D₅W at 0.5-1 cc/min)
or Lidocaine 50 mg IV bolus (0.5 mg/kg) May repeat every 5 mins until total dose 225 mg given
if NSR*
Continue as directed by Medical Control until transport completed

Pulse present, unconscious

A. Lidocaine 100 mg (1 mg/kg) IV

B. Cardioversion 200 joules (synchronous countershock)
Check pulse — if reversion to normal rhythm proceed to step 3.

C. If continued ventricular tachycardia, pulse present, patient unconscious
Bretylium 350-500 mg IV (5 mg/kg) over 8-10 min
Check pulse — if reversion to normal rhythm proceed to step 3.

D. If no change, cardioversion 200 joules
Check pulse — if reversion to normal rhythm proceed to step 3.

E. If no change, Bretylium 700-1000 mg IV (10 mg/kg) and Infusion 1-2 mg/min (500 mg in 250 cc D_5W) at 0.5-1 cc/min or Lidocaine 50 mg IV (0.5 mg/kg). May repeat Lidocaine 50 mg every 5 min until 225 mg total dose given

F. Follow these steps as directed by Medical Control until transport completed

3. If rhythm reverts to sinus give Lidocaine infusion (1 gm in 250 cc D_5W = 4 mg/cc) at 0.5-1 cc/min with repeat boluses 50-75 mg every 5-10 min to 225 mg maximum until transport completed.

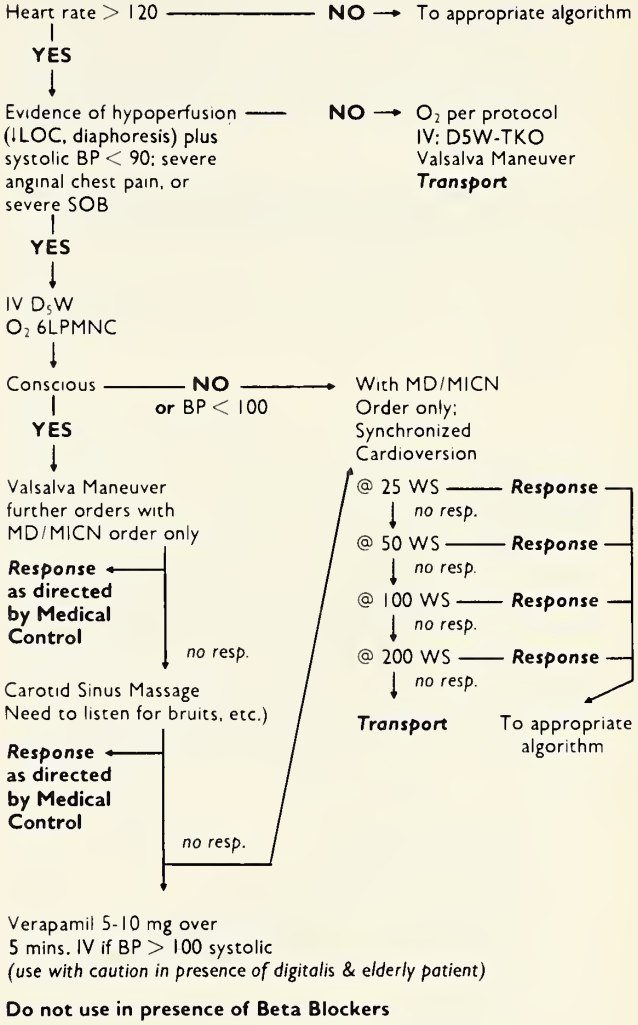
Treatment Protocol B-0-2
(Pulmonary Edema Associated with Acute Myocardial Infarction)

1. Recognize pulmonary edema in the setting of acute myocardial infarction: typical chest pain, diaphoresis, marked dyspnea, pulmonary râles.
2. Follow Protocol B-0. If significant hypotension (systolic pressure <90) is present treat according to Protocol B-0-3 before going to steps 3-5 below.
3. If BP >100s, NTG 1/150 SL — may repeat in 5 minutes
4. Lasix 20-40 mg IV slow push
5. Monitor and advise Medical Control of changes until transport is completed.

Treatment Protocol B-0-3
(Hypotension/Shock Associated with Acute Myocardial Infarction)

1. Recognize shock/hypotension in the setting of acute myocardial infarction: typical chest pain, diaphoresis, systolic pressure of 40-90, cool moist extremities, dyspnea of varying severity.
2. Assess volume status. If hypovolemia is suspected and the patient does *not* have pulmonary edema, give a single volume infusion of Ringer's lactate (100-200 cc over 5-10 minutes).[a]
3. Follow Protocol B-0 and begin step 4 below.
4. Begin Dopamine infusion to maintain systolic pressure at 80-90.[b]
5. Continue these steps until transport is completed.

SUPRAVENTRICULAR TACHYCARDIAS
(Includes PAT, Rapid Atrial Fib. or Atrial Flutter)


Heart rate > 120
NO
To appropriate algorithm
YES
Evidence of hypoperfusion (↓LOC, diaphoresis) plus systolic BP < 90; severe anginal chest pain, or severe SOB
NO
O₂ per protocol
IV: D5W-TKO
Valsalva Maneuver
Transport
YES
IV D₅W
O₂ 6LPMNC
Conscious
NO
or BP < 100
With MD/MICN Order only; Synchronized Cardioversion
YES
Valsalva Maneuver further orders with MD/MICN order only
Response as directed by Medical Control
no resp.
Carotid Sinus Massage Need to listen for bruits, etc.)
Response as directed by Medical Control
no resp.
@ 25 WS
Response
no resp.
@ 50 WS
Response
no resp.
@ 100 WS
Response
no resp.
@ 200 WS
Response
no resp.
Transport
To appropriate algorithm
Verapamil 5-10 mg over 5 mins. IV if BP > 100 systolic
(use with caution in presence of digitalis & elderly patient)
Do not use in presence of Beta Blockers

Treatment Protocol B-0-4
Supraventricular Tachycardia Including PAT, Rapid Atrial Fibrillation or Atrial Flutter

A. General assessment
Specific observation:
   1. Lung sounds
   2. Rule out supraventricular tachycardia due to other causes

B. Initial emergency care
   1. Establish and maintain airway with oxygen and *assure adequate ventilation*
   2. Establish IV as necessary with D_5W at KVO rate
   3. Connect to monitor

C. Establish communications with Medical Control base station
   1. Transmit EKG

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[a] In patients with true cardiogenic shock the pulmonary circuit is invariably overloaded which volume infusion may worsen. Other types of shock (hypovolemic,[1] right ventricular infarction[2]), however, will be improved by volume infusion.

1. Forrester JS et al. Medical therapy of acute myocardial infarction by application of hemodynamic subsets. N Eng J Med 1976;295:1356-62.
2. Lorell B et al. Right ventricular infarction. Am J Cardiol 1979;43:465-71.

[b] Dopamine infusion (200 mg in 250 cc D_5W = 800 mcg/cc). Begin at 0.5 cc/min and titrate.

D. Definite care by physician order via voice communications
   1. Valsalva maneuver while transmitting EKG
   2. Unilateral carotid massage; check for bruits first
   3. Transmit EKG to Medical Control with repeat transmit EKG
   4. Consider use of Verapamil 5-10 mg over 5 minutes IV if BP more than 100s. **DO NOT** use Verapamil in presence of beta blocker; use with caution in presence of digitalis and in elderly.
   5. In consultation with Medical Control, consider cardioversion, beginning 25-50 ws, in patient with deteriorating level of consciousness or hypotension BPs <100.

Treatment Protocol B-0-5
Mobitz Type II or Complete Heart Block

A. Initial emergency care
   1. Establish and maintain airway with oxygen and *assure adequate ventilation.*
   2. See appropriate S.O.P. for Suspected MI

B. Establish communications with Medical Control and base station
   1. Transmit EKG

C. Definitive care by physician order via voice communications
   1. Transmit EKG to Medical Control — observe for changes
   2. Atropine Sulfate .5-1 mg IV push — May be repeated every 5 min. Total dosage not to exceed 2 mg.
   3. Transmit EKG to Medical Control — observe for changes
   4. Isuprel (Isoproterenol) drip (Isuprel 2 mg in 500 cc D_5W) to maintain heart rate of 60-100 or BP of 90 systolic. *Isuprel to be used only for complete heart block.*
   5. Continue to monitor and transport.

Treatment Protocol C-0

Prehospital Treatment of Coma of Unknown Cause

A. **Definition** — Coma is a state in which the patient is incapable of sensing or responding to external stimuli and appears to be asleep. A whole spectrum of altered states of consciousness exist between the extremes of normal consciousness and coma: drowsiness, stupor, confusion, and delirium. These all may reflect pathogenic mechanisms similar to coma and should be approached in much the same manner.

B. **Etiology** — Coma can be divided into *intracranial* and *extracranial* causes. Common causes in each category include:
   1. Intracranial causes
      a. Subdural hematoma
      b. Epidural hematoma
      c. Subarachnoid hemorrhage
      d. Traumatic cerebral hemorrhage/edema
      e. Nontraumatic cerebral hemorrhage/edema
      f. Stroke
      g. Meningitis
      h. Encephalitis
      i. Brain abscess
      j. Neoplasm
   2. Extracranial causes
      a. Toxic causes (alcohol, sedatives, tricyclics, barbiturates, etc.)
      b. Metabolic causes
         1. Electrolyte disorders
         2. Hypoglycemia
         3. Hyperglycemia
         4. Hypoxia
         5. Uremic coma
         6. Hepatic coma
         7. Myxedema
         8. Addison's disease
      c. Hypertensive encephalopathy

C. **Diagnosis** — When a head injury is the cause of coma there is usually obvious external evidence of it. At times however, there may be very minimal or no evidence of an injury. A high index of suspicion must be maintained in all comatose patients.

In metabolic or toxic coma focal neurologic findings are usually absent. Hypoglycemia may present with focal findings. The smell of alcohol on the breath however, should not deter one from considering other causes for the coma (subdural/epidural hematomas, hypoglycemia, drug overdose, etc.).

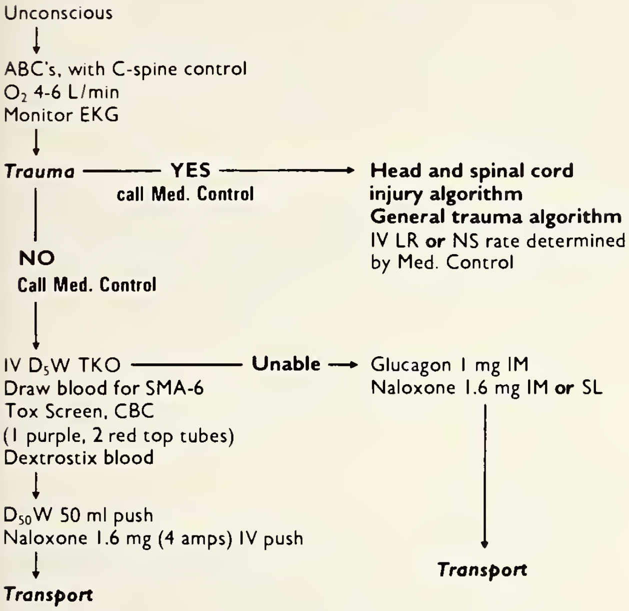
When focal neurologic signs are present an intracranial process is most likely. The most common intracranial disorders with focal findings are traumatic intracranial hemorrhage, stroke, tumor, and brain abscess.

Treatment Protocol C-0
(Coma of Unknown Cause)

1. Recognize coma and note any evidence of trauma.
2. Protect and immobilize the cervical spine.
3. Open and maintain the airway.
4. Administer O_2 by mask or nasal prongs at 6 L/min.
5. If trauma is present stop active bleeding, decompress tension pneumothorax, etc. (see trauma protocol(s)).
6. Monitor cardiac activity.
7. Draw blood for CBC, SMA-6, and toxicology screen (1 purple, 2 red top tubes). Perform Chemstik or Dextrostix for baseline glucose level. Call Medical Control.
8. Place IV line. Infuse:
   A. D_5W at KVO if no suspicion of trauma or
   B. Lactated Ringer's at variable rate if trauma is suspected or hypotension is present.
9. If coma appears most likely due to a nontraumatic cause or if hypoglycemia is documented on the Dextrostick give in sequence:
   A. Dextrose (50 cc of 50% solution) IV push or if can't establish IV Glucagon 1 mg IM.
   B. Narcan (4 amps, 1.6 mg) IV push.

10. Continue supportive measures until transport is completed.

COMA OR ALTERED LEVEL OF CONSCIOUS ALGORITHM



Treatment Protocol C-1
Prehospital Treatment of Poisoning

A. **Definition** — Approximately 90 percent of all poisonings are accidental, occur in toddlers between the ages of 18 months and three years, and are not life-threatening. Serious drug ingestions are usually deliberate, due to suicidal or homicidal intent.

B. **Etiology** — Poisoning in children is a function of the drugs and toxic materials found in their environment. In teenagers and adults it is usually an intentional act and often involves alcohol as an additional toxin. The commonest drugs (after alcohol) ingested seriously by adults in decreasing order of frequency are:[a]

1. Valium
2. Salicylates
3. Tricyclics
4. Psychedelics (marijuana, LSD)
5. Narcotics
6. Acetaminophen
7. Barbiturates
8. Others

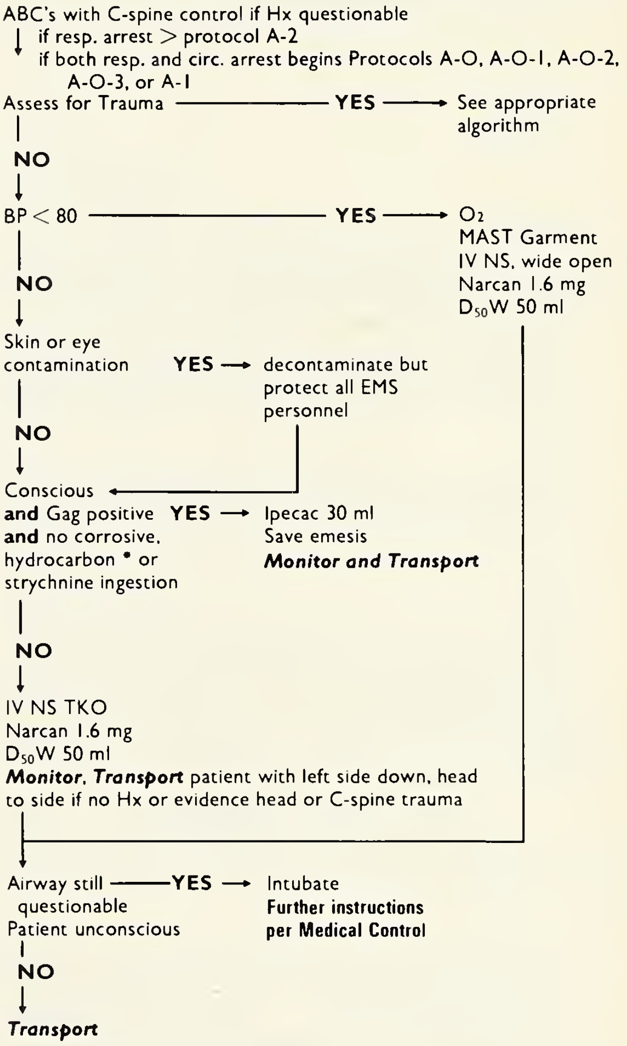
Poisoning also may occur by routes of exposure other than ingestion. The percentages of frequencies[a] are:

1. Oral — 87.4%
2. Ophthalmic — 4.1%
3. Dermal — 3.7%
4. Inhalation — 2.9%
5. Injection — 0.3%

C. **Diagnosis** — Occasionally the ingestion is unwitnessed and the patient's condition may be categorized as coma of unknown origin. Friends and relatives, however, are frequently available who have observed or know of the ingestion. The physical examination may give a clue to the type of ingestion:

1. *Abnormal odor on breath:* alcohol, acetone, wintergreen, etc.
2. *Hyperventilation:* salicylates, atropine, cocaine, cyanide, camphor, etc.
3. *Dilated pupils:* atropine, alcohol, cocaine, amphetamines, LSD, etc.
4. *Constricted pupils:* morphine and other narcotics, organophosphates, barbiturates, etc.

POISONING AND OVERDOSE ALGORITHM


ABC's with C-spine control if Hx questionable
if resp. arrest > protocol A-2
if both resp. and circ. arrest begins Protocols A-O, A-O-1, A-O-2, A-O-3, or A-1
Assess for Trauma
YES
See appropriate algorithm
NO
BP < 80
YES
O₂
MAST Garment
IV NS, wide open
Narcan 1.6 mg
D₅₀W 50 ml
NO
Skin or eye contamination
YES
decontaminate but protect all EMS personnel
NO
Conscious and Gag positive and no corrosive, hydrocarbon * or strychnine ingestion
YES
Ipecac 30 ml
Save emesis
Monitor and Transport
NO
IV NS TKO
Narcan 1.6 mg
D₅₀W 50 ml
Monitor, Transport patient with left side down, head to side if no Hx or evidence head or C-spine trauma
Airway still questionable
Patient unconscious
YES
Intubate
Further instructions per Medical Control
NO
Transport

*unless carrier for more toxic agent

Treatment Protocol C-1
(Poisoning)

1. Recognize poisoning: history from family or friends, bottles, containers, etc., abnormal breath odor, constricted or dilated pupils, or altered state of consciousness.

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[a] Litovitz TL. Poison center operations: the necessity of follow-up. Ann Emerg Med 1982;11:348-52.

2. Open the airway and assist ventilation if necessary as outlined in Protocol A-2. Check for gag reflex.
3. Check peripheral pulse (carotid).
   - A. If breathing is arrested but circulation is present begin Protocol A-2.
   - B. If both breathing and circulation are arrested begin Protocols A-0, A-0-1, A-0-2, A-0-3, or A-1.
   - C. If both breathing and circulation are present proceed as below.
4. Obtain history from friends, relatives, observers. Bring any containers along during transport.
5. If there is evidence of external contamination:
   - A. Protect all EMS personnel.
   - B. Remove contaminated clothing.
   - C. Flush skin and eyes with copious amounts of water.
6. If there is evidence of internal ingestion and the patient is awake and alert administer Ipecac, except in the following where emesis is contraindicated:[a, b]
   - A. Suspected ingestion of strong acids, strong bases, or hydrocarbons or strychnine (unless carrier for more toxic agent).
   - B. An unconscious patient or patient with decreasing level of consciousness.
7. Place IV line. Infuse D_5W at KVO rate. Draw purple top, 2 red top tubes.
8. If patient is comatose proceed with Protocol C-0.
9. Continue supportive measures until transport is completed.

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[a] Ipecac dose: 30 cc in adults and 15 cc in children. Copious oral fluids should be administered along with the Ipecac. All emesis should be saved and delivered to the Emergency Department.

[b] When in doubt about inducing emesis call for advice to on-line Medical Control or to the Duke Poison Center, 1-800-672-1697.

Treatment Protocol D-0

Prehospital Treatment of Severe Trauma

A. **Definition** — Trauma is the leading cause of death between the ages of one and 40 years. Studies have clearly demonstrated that advanced life support in the field and rapid delivery to, and treatment in, a sophisticated trauma center markedly enhance survival. It is estimated that up to 50 percent of severe trauma deaths are preventable, provided the patient receives optimal care.

B. **Etiology** — A close second in terms of morbidity and mortality is blunt deceleration injuries (usually due to vehicular accidents). The cause of most fatal traumatic injuries is penetrating wounds to the chest and abdomen.

C. **Diagnosis** — The diagnosis of severe trauma is neither subtle nor difficult. One must maintain a high index of suspicion for certain immediate life-threatening entities (tension pneumothorax, etc.) and establish priorities in the evaluation and immediate treatment of these patients.

Trauma Physical Examination

Follow all medical criteria; protect the cervical spine and assess as follows in the order given.

Primary Survey

1. *Vital Signs:* Pulse, systolic blood pressure, respiratory rate, respiratory expansion and capillary refill.
2. *Neurological Assessment:* (Glascow Coma Scale) eye opening, verbal response, motor response. (see appendix) AVPU
   STOP
3. Report the above elements and the mechanism of injury. Continue with assessment.

Secondary Survey

4. *Head and Face:* Wounds, depressions, deformities, blood or fluid from ears or nose, bruises around eyes and/or behind the ears.
5. *Neck:* Tracheal deviation, wounds, protrusions of the spine, bruises, crepitus (subcutaneous emphysema).
6. *Chest:* Wounds, bruises, flail chest, heart sounds, breath sounds, presence of bowel sounds, crepitus (subcutaneous emphysema), sucking chest wounds.
7. *Back:* Wounds, bruises, crepitus (subcutaneous emphysema).
8. *Abdomen:* Wounds, bruises, rigidity, distention, bowel sounds.
9. *Pelvis:* Crepitus or pain on pressure.
10. *Extremities:* Wounds, fractures, dislocation, motor sensory loss, positioning pulses, temperature and color.

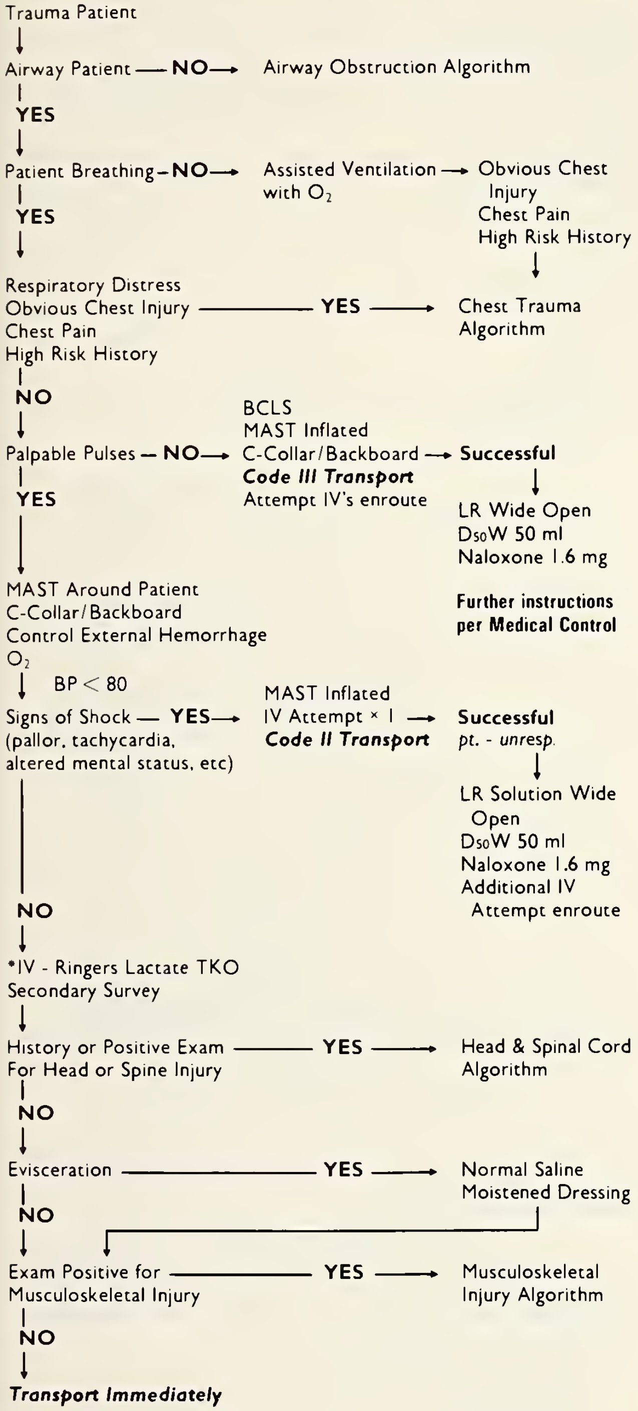
REPORT COMPLETE ASSESSMENT

Complete assessment should be reported within 3 minutes.

Treatment Protocol D-0
(Severe Trauma)

1. Recognize severe trauma: combined system injury, uncontrolled hemorrhage, severe face/head and neck injuries, unstable chest injuries, blunt or penetrating abdominal trauma with hypotension, prolonged loss of consciousness with localizing neurological signs, etc. In these patients time is critical and transport should not be delayed for field resuscitation. Call Medical Control immediately which may advise immediate transport in a short "run."
2. Open the airway to assist ventilation if necessary as outlined in Protocol A-2 but at the same time maintain in-line traction on the cervical spine and immobilize.
3. Check peripheral pulse (carotid).
   - A. If breathing and circulation are absent begin Protocols A-0, A-0-1, A-0-2, A-0-3, or A-1.[a]
4. Identify hemorrhage and control by direct pressure on the wound.
5. Begin O_2 by mask or nasal prongs at 6 L/min.
6. Seal sucking chest wound if present.
7. Apply MAST garment if systolic pressure is <90 or if

PRE-HOSPITAL CARE OF TRAUMA: GENERAL MANAGEMENT ALGORITHM

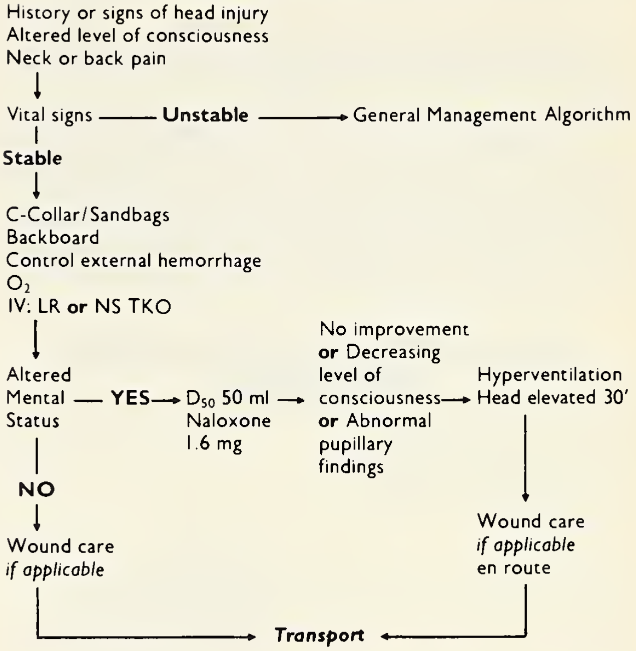


**All patients with the potential for serious injury should have an IV started unless transport time to the hospital is 2-3 minutes.*

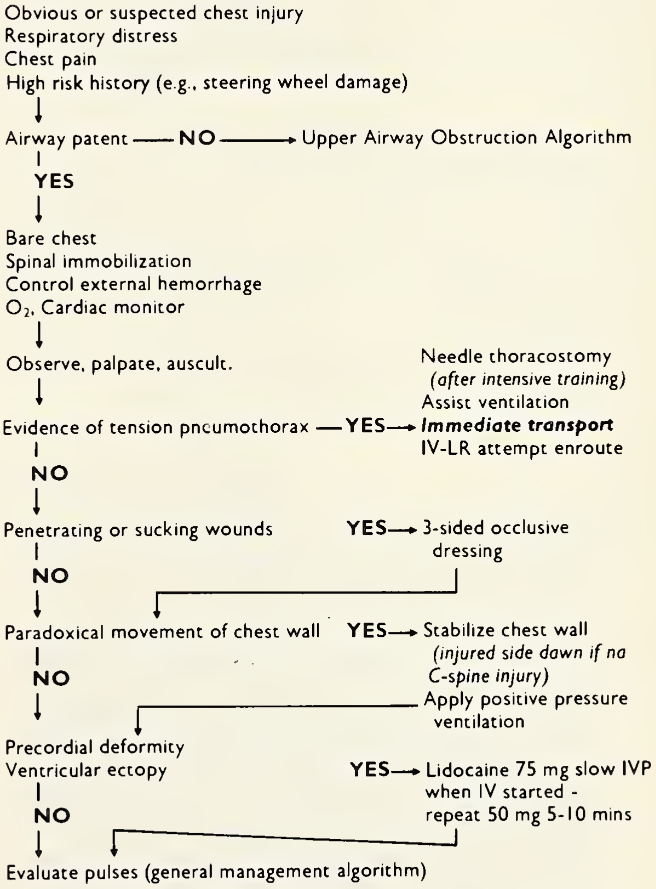
IV cannot be started immediately.

8. Place two large-bore IV lines and draw blood for CBC, SMA-6, and type and cross (1 purple, 2 red top tubes). Begin Ringer's lactate or NS and infuse rapidly until systolic pressure is 90 or above, then titrate to maintain this pressure.[b]
9. Relieve tension pneumothorax if present. (See Protocol D-1)

PRE-HOSPITAL CARE OF TRAUMA: HEAD & SPINAL CORD


History or signs of head injury
Altered level of consciousness
Neck or back pain
Vital signs
Unstable
General Management Algorithm
Stable
C-Collar/Sandbags
Backboard
Control external hemorrhage
O2
IV: LR or NS TKO
Altered Mental Status
YES
D50 50 ml
Naloxone 1.6 mg
No improvement or Decreasing level of consciousness or Abnormal pupillary findings
Hyperventilation
Head elevated 30'
NO
Wound care if applicable
Wound care if applicable en route
Transport

PRE-HOSPITAL CARE OF TRAUMA: CHEST


Obvious or suspected chest injury
Respiratory distress
Chest pain
High risk history (e.g., steering wheel damage)
Airway patent
NO
Upper Airway Obstruction Algorithm
YES
Bare chest
Spinal immobilization
Control external hemorrhage
O2, Cardiac monitor
Observe, palpate, auscult.
Evidence of tension pneumothorax
YES
Needle thoracostomy (after intensive training)
Assist ventilation
Immediate transport
IV-LR attempt enroute
NO
Penetrating or sucking wounds
YES
3-sided occlusive dressing
NO
Paradoxical movement of chest wall
YES
Stabilize chest wall (injured side down if no C-spine injury)
Apply positive pressure ventilation
NO
Precordial deformity
Ventricular ectopy
YES
Lidocaine 75 mg slow IVP when IV started - repeat 50 mg 5-10 mins
NO
Evaluate pulses (general management algorithm)

10. Intubate (E-T, N-T, or EOA) if necessary. Every effort must be made to avoid manipulating the neck in those with suspected cervical spine injuries.
11. Monitor cardiac activity.

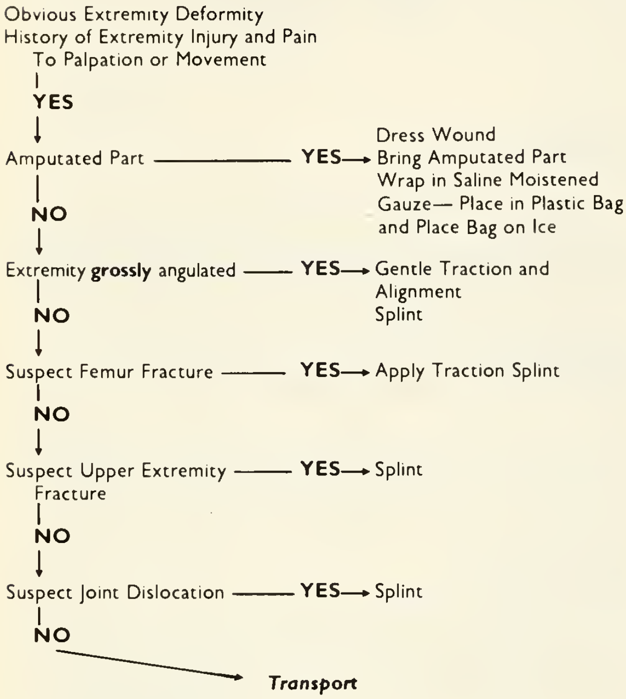
12. Splint fractures.
13. Continue these steps until transport is completed.

---

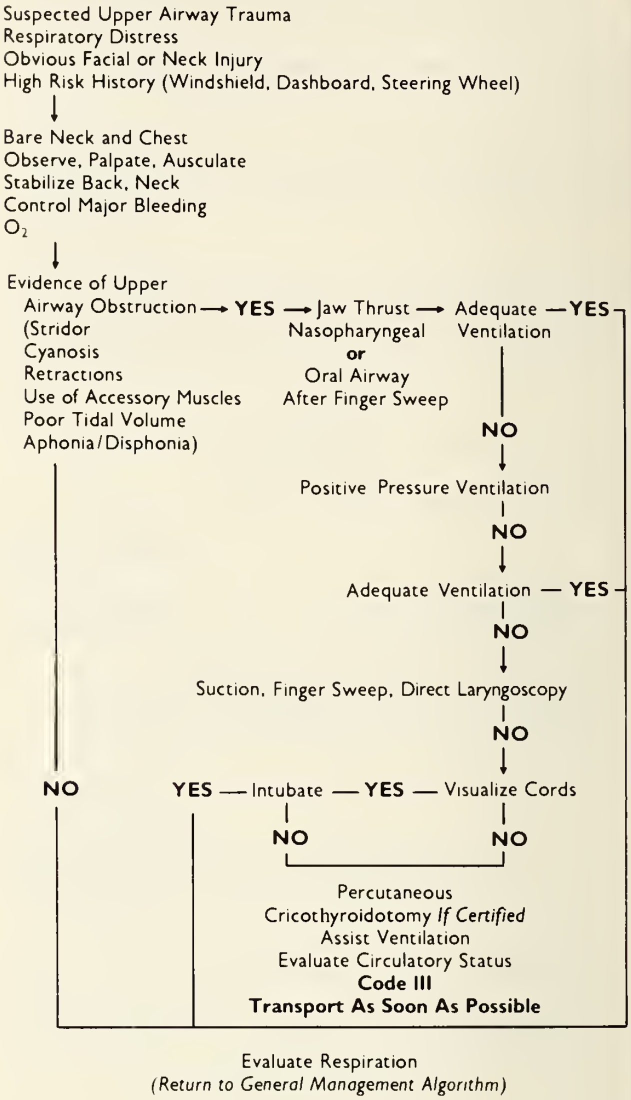
[a] In traumatic cardiac arrest time constraints are a major determinant of mortality. Resuscitation should be carried out *without* delaying transport.

[b] Infusion should proceed systematically with sequential boluses of 250 cc at 5-10 minute intervals in those with systolic pressures <90. In the patient who has an associated, severe head injury the shock-state should be treated as if hemorrhagic shock were the cause. Caution, however, must be practiced in the setting of severe head injury without evidence of shock. Careless volume infusion in this situation could worsen cerebral edema. If head injury without shock is the major impression, NS or RL should be infused at KVO rate.

PRE-HOSPITAL CARE OF TRAUMA: EXTREMITIES


Obvious Extremity Deformity
History of Extremity Injury and Pain To Palpation or Movement
YES
Amputated Part
YES
Dress Wound
Bring Amputated Part
Wrap in Saline Moistened Gauze— Place in Plastic Bag and Place Bag on Ice
NO
Extremity grossly angulated
YES
Gentle Traction and Alignment
Splint
NO
Suspect Femur Fracture
YES
Apply Traction Splint
NO
Suspect Upper Extremity Fracture
YES
Splint
NO
Suspect Joint Dislocation
YES
Splint
NO
Transport

UPPER AIRWAY TRAUMA/OBSTRUCTION ALGORITHM


Suspected Upper Airway Trauma
Respiratory Distress
Obvious Facial or Neck Injury
High Risk History (Windshield, Dashboard, Steering Wheel)
Bare Neck and Chest
Observe, Palpate, Ausculate
Stabilize Back, Neck
Control Major Bleeding
O2
Evidence of Upper Airway Obstruction
(Stridor
Cyanosis
Retractions
Use of Accessory Muscles
Poor Tidal Volume
Aphonia/Disphonia)
YES
Jaw Thrust
Nasopharyngeal
or
Oral Airway
After Finger Sweep
Adequate Ventilation
YES
NO
Positive Pressure Ventilation
NO
Adequate Ventilation
YES
NO
Suction, Finger Sweep, Direct Laryngoscopy
NO
NO
YES
Intubate
YES
Visualize Cords
NO
NO
Percutaneous
Cricothyroidotomy If Certified
Assist Ventilation
Evaluate Circulatory Status
Code III
Transport As Soon As Possible
Evaluate Respiration
(Return to General Management Algorithm)

Treatment Protocol D-1

Prehospital Treatment of Tension Pneumothorax

A. **Definition** — Tension pneumothorax is an immediate life-threatening condition in which air progressively accumulates in the pleural space due to a one-way valve air leak. The lung is compressed. The mediastinal contents are forced toward the opposite hemithorax. This impairs ventilation. Decreased cardiac output follows as the venae cavae become angulated at their junction with the right atrium. Decreased effective tissue oxygenation leads to lactic acidosis. Lactic acidosis further depresses cardiac output. Death occurs rapidly unless pleural decompression is carried out.

B. **Etiology** — The most common entities resulting in tension pneumothorax are:
   1. Blunt chest trauma.
   2. Spontaneous pneumothorax in which the ruptured bleb has failed to seal.
   3. Mechanical ventilation with positive end-expiratory pressure (PEEP).

C. **Diagnosis** — The five classic signs and symptoms of tension pneumothorax are:
   1. Respiratory distress.
   2. Cyanosis.
   3. Absence of breath sounds of the side of the pneumothorax.
   4. Tracheal deviation to the side opposite the pneumothorax.
   5. Distended neck veins.

Occasionally massive hemothorax or pericardial tamponade may be confused with tension pneumothorax. The former is distinguished by a dull percussion note over the hemithorax. The latter is distinguished by the presence of bilateral breath sounds.

Treatment Protocol D-1
(Tension Pneumothorax)

1. Recognize tension pneumothorax: respiratory distress, cyanosis, distended neck veins, tracheal deviation, absent breath sounds.
2. Call Medical Control. Begin immediate transport if field decompression warranted.

Method of Pleural Decompression (14 gauge over-the-needle catheter)

A. Prep the second intercostal space-midclavicular line on the side of the tension with Betadine.
B. Draw 5 cc of sterile IV solution into a 50 cc syringe and attach to a 14 gauge over-the-needle catheter (6 cm length).
C. Insert the needle just above the rib in the second intercostal space-midclavicular line on the side of the tension until a "pop" is felt.
D. Aspirate to demonstrate withdrawal of air.
E. Thread catheter and remove needle and syringe. Secure with tape.
F. Connect hub of catheter to a one-way flutter valve *or* to IV tubing, the free end of which is placed in a dependent bottle of sterile IV solution.

Treatment Protocol D-2

Prehospital Treatment of Burn

A. **Definition** — The care of the seriously burned patient is primarily conducted in the hospital. Burns are classified into: (1) *First-degree* which consists of simple redness and tenderness but with no death of epithelium; (2) *Second-degree* which may be either superficial or deep and is indicated by the presence of blisters; and (3) *Third-degree* which is a full-thickness burn and appears as dry, white, or charred skin.

B. **Etiology** — Burns may be caused by any variety of combustible substances or transmission of electrical currents through the body. Early mortality is most often due to hypovolemic shock (secondary to enormous fluid losses) and hypoxia (secondary to respiratory tract involvement). Late mortality is most often the result of sepsis.

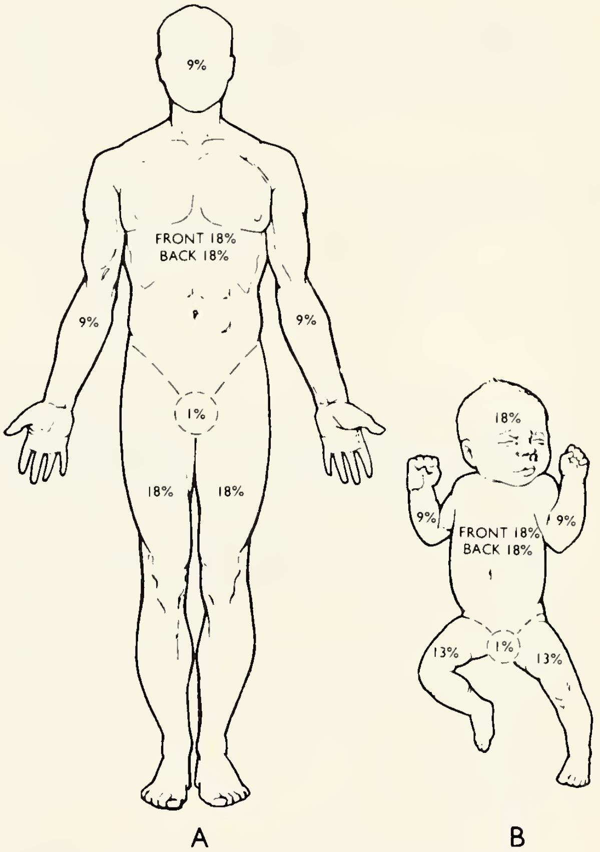
C. **Diagnosis** — The scenario of the burn is important information in evaluating a patient. The patient who is burned in an enclosed room is likely to have respiratory tract damage. Burns following vehicular accidents are almost always compounded by other injuries. Hot metal or oil produces a deeper burn than does hot water. The area of burn visible after an electrical injury is always less than that which indeed exists. The time interval between burning and the appearance of serious complications (shock and respiratory distress) may be delayed 30-60 minutes or more.

In describing the degree of burn to Medical Control, it is helpful to estimate the body surface area involved. This is accomplished by utilizing the "rule of nines" for adults. The "rule of nines" is adapted for children, who have a relatively larger head size than adults.

Furthermore, burned patients may have other injuries that should be evaluated and may take precedence over burns themselves.

Treatment Protocol D-2
(Burn)

1. Recognize burn injury and assess its severity.



Kravis and Warner. **Emergency Medicine, A Comprehensive Review.** Aspen Systems Corp., 1983, Page 299.

Major Burns (those requiring treatment in a burn center or burn unit) should be considered as any of the following:

1. **Third-degree burns involving more than 10% of the total body surface.**
2. **Partial-thickness (deep second-degree) burns involving more than 20% of the total body surface.**
3. **Any serious burns of the hands, feet, or anogenital region.**
4. **Burns associated with multiple, severe trauma.**
5. **High voltage electrical burns.**
6. **Inhalation injury and burns about the face and mouth.**
7. **Any type burns in patients with serious underlying medical problems.**

2. Extinguish any fire and move patient away from the heat into a ventilated area.
3. Open the airway and assist ventilation if necessary as outlined in Protocol A-2. If evidence of smoke inhalation or airway burn begin O_2 by non-rebreathing mask at 15 L/min.
4. Begin O_2 by mask or nasal prongs at 6 L/min. Call Medical Control.
5. Attend to other associated major injuries as outlined in Protocol D-0. If Hx of ingestion, intoxication — attend to these as outlined in Protocol C-1.
6. Place IV line in unburned extremity if at all possible. Begin Ringer's lactate and infuse rapidly until systolic pressure is 90 or above, then titrate to maintain this pressure.[a] (Follow Protocol E-0 if shock is present).
7. Monitor cardiac activity.
8. If possible, remove clothing and all other restrictive articles (rings, bracelets, etc.)
9. Wrap burn area in sterile saline dressings or use sterile burn pack.
10. If available consider Morphine Sulfate 2-5 mg IV q 5 min prn.
11. Continue these supportive measures until transport is completed.

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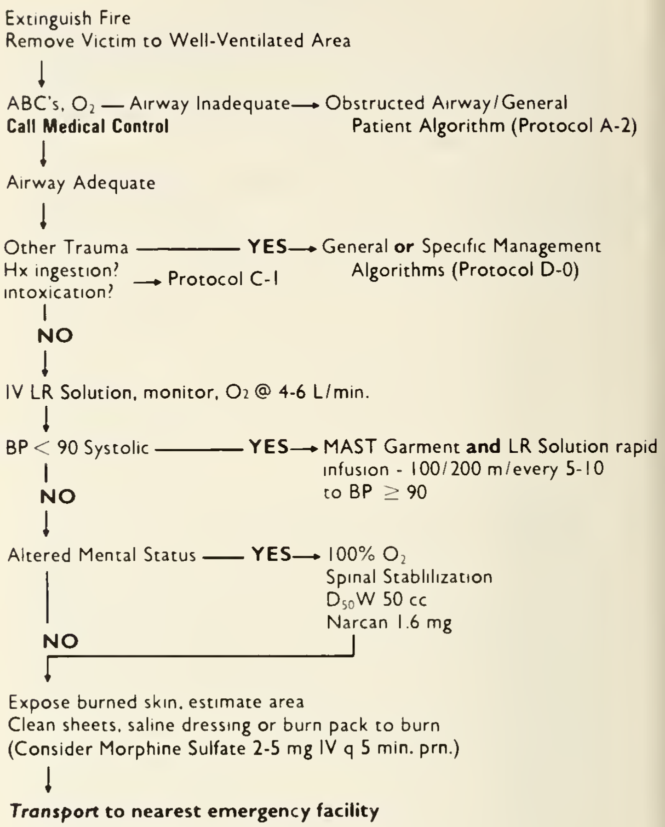
[a] Infusion should proceed systematically with sequential boluses of 100-200 cc at 5-10 minute intervals until the systolic pressure is 90 or above.

PRE-HOSPITAL CARE OF TRAUMA: BURNS


Extinguish Fire
Remove Victim to Well-Ventilated Area
ABC's, O_2 — Airway Inadequate → Obstructed Airway/General Patient Algorithm (Protocol A-2)
Call Medical Control
Airway Adequate
Other Trauma — YES → General or Specific Management Algorithms (Protocol D-0)
Hx ingestion? intoxication? → Protocol C-1
NO
IV LR Solution, monitor, O_2 @ 4-6 L/min.
BP < 90 Systolic — YES → MAST Garment and LR Solution rapid infusion - 100/200 m/every 5-10 to BP ≥ 90
NO
Altered Mental Status — YES → 100% O_2
Spinal Stabilization
$D_{50}W$ 50 cc
Narcan 1.6 mg
NO
Expose burned skin, estimate area
Clean sheets, saline dressing or burn pack to burn
(Consider Morphine Sulfate 2-5 mg IV q 5 min. prn.)
Transport to nearest emergency facility

Prehospital Treatment of Shock

A. **Definition** — Shock is a state of circulatory insufficiency which can be caused by many entities. The relative or absolute hypovolemia or decreased cardiac output leads to the underperfusion of tissues of the body, with resultant lack of oxygen and other nutrients necessary for cellular metabolism and lack of removal of toxic waste materials.

B. **Etiology** — Shock may be classified according to the underlying etiology. The major categories include:
   1. Hypovolemic shock — the most common etiology
   2. Cardiogenic shock — see cardiac protocols
   3. Septic shock
   4. Neurogenic shock
   5. Anaphylactic shock
   6. Miscellaneous etiologies (pulmonary embolism, heat stroke, cardiac tamponade, metabolic causes, etc.)

C. **Diagnosis** — The history may be helpful. There may be a history of trauma, peptic ulcer disease, esophageal varices, burn, or excessive vomiting or diarrhea in the case of hypovolemic shock.

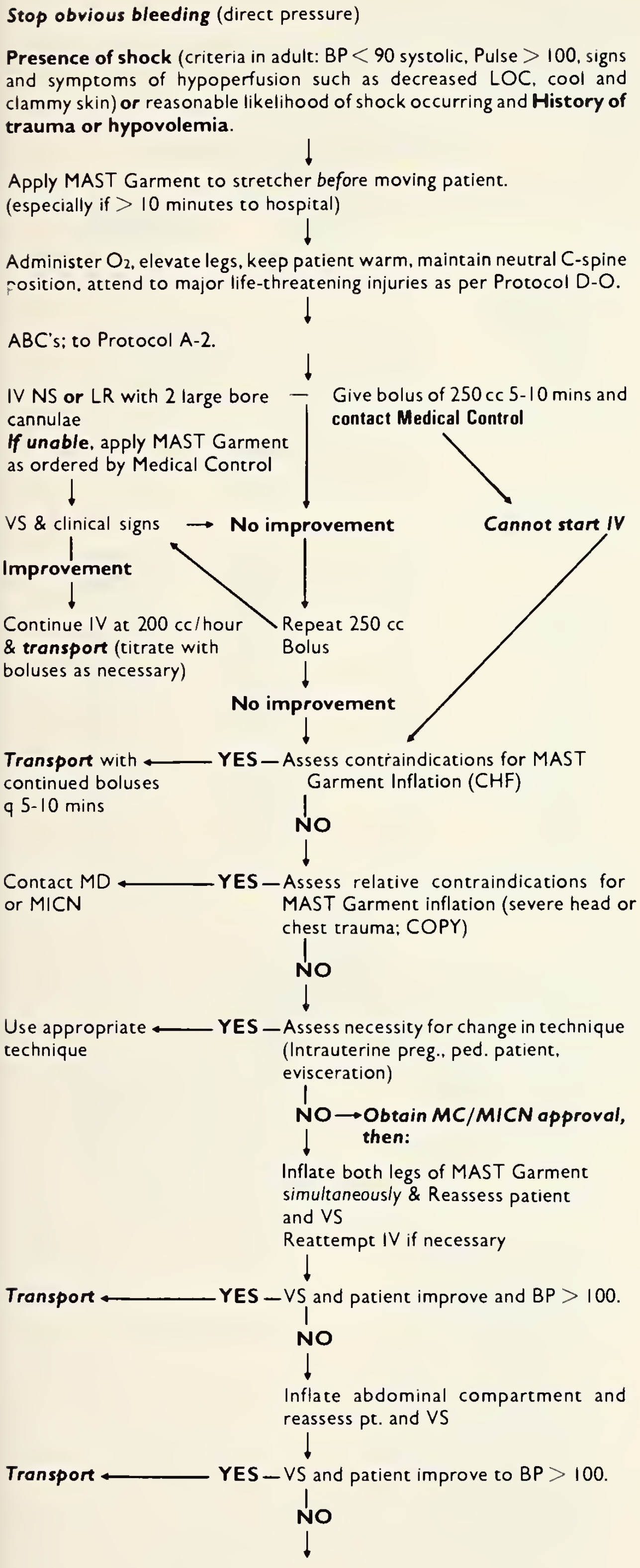
There may be a history of typical chest pain suggesting an acute myocardial infarction in the case of cardiogenic shock. There may be a past history of allergic reactions and recent exposure to drugs, insect bites, vaccines, or diagnostic agents (such as IVP dye) in the case of anaphylactic shock. The diagnosis is usually not difficult, except in the early stages of the shock syndrome when merely tachycardia or tachypnea may be present. In the elderly the diagnosis may be extremely subtle; a confused mental state may be the only clue.

The classic presentation, however, is not to be confused with anything else:
1. Tachycardia
2. Hypotension
3. Tachypnea
4. Weak, thready peripheral pulse
5. Fever (in the case of septic shock)
6. Cool, sweaty skin
7. Decreased urine output

Treatment Protocol E-0
(Shock, Hypovolemic)

1. Recognize the shock state and suspect hypovolemia as its cause.
2. Open the airway and assist ventilation if necessary as outlined in Protocol A-2.
3. Maintain neutral position of the cervical spine and immobilize if there is evidence of trauma.
4. Attend to other associated major injuries as outlined in Protocol D-0, including arresting external hemorrhage with direct pressure, and contact Medical Control.
5. Begin O_2 by mask or nasal prongs at 6 L/min.
6. Position patient supine with legs elevated.

HYPOTENSION PROTOCOL
(Trauma/Hypovolemia)


Stop obvious bleeding (direct pressure)
Presence of shock (criteria in adult: BP < 90 systolic, Pulse > 100, signs and symptoms of hypoperfusion such as decreased LOC, cool and clammy skin) **or** reasonable likelihood of shock occurring and **History of trauma or hypovolemia**.
Apply MAST Garment to stretcher *before* moving patient. (especially if > 10 minutes to hospital)
Administer O₂, elevate legs, keep patient warm, maintain neutral C-spine position, attend to major life-threatening injuries as per Protocol D-O.
ABC's; to Protocol A-2.
IV NS **or** LR with 2 large bore cannulae
If unable, apply MAST Garment as ordered by Medical Control
Give bolus of 250 cc 5-10 mins and **contact Medical Control**
VS & clinical signs
No improvement
Cannot start IV
Improvement
Continue IV at 200 cc/hour & ***transport*** (titrate with boluses as necessary)
Repeat 250 cc Bolus
No improvement
Transport with continued boluses q 5-10 mins
YES
Assess contraindications for MAST Garment Inflation (CHF)
NO
Contact MD or MICN
YES
Assess relative contraindications for MAST Garment inflation (severe head or chest trauma; COPY)
NO
Use appropriate technique
YES
Assess necessity for change in technique (Intrauterine preg., ped. patient, evisceration)
NO ***Obtain MC/MICN approval, then:***
Inflate both legs of MAST Garment *simultaneously* & Reassess patient and VS
Reattempt IV if necessary
Transport
YES
VS and patient improve and BP > 100.
NO
Inflate abdominal compartment and reassess pt. and VS
Transport
YES
VS and patient improve to BP > 100.
NO

Continue inflating *first* the legs, *then* the abdomen until improvement in patient and VS occurs **or** until pressure limit of the suit is reached (104 mmHg). **Unless the patient *dramatically* deteriorates after MAST garment inflation, DO NOT deflate suit in the field.**

7. Place two large-bore IV lines. Begin Ringer's lactate or NS and infuse rapidly[a] until systolic pressure is 90 or above, then titrate to maintain this pressure. May try maintenance at 150-200 cc/hour.
8. Apply MAST garment if systolic pressure is <90 or if IV cannot be started immediately. (Assess and relay contraindications to Medical Control.)
9. Monitor cardiac activity.
10. Continue these measures until transport is completed.

---

[a] Infusion should proceed systematically with sequential boluses of 250 cc at 5-10 minute intervals until the systolic pressure is 90 or above.

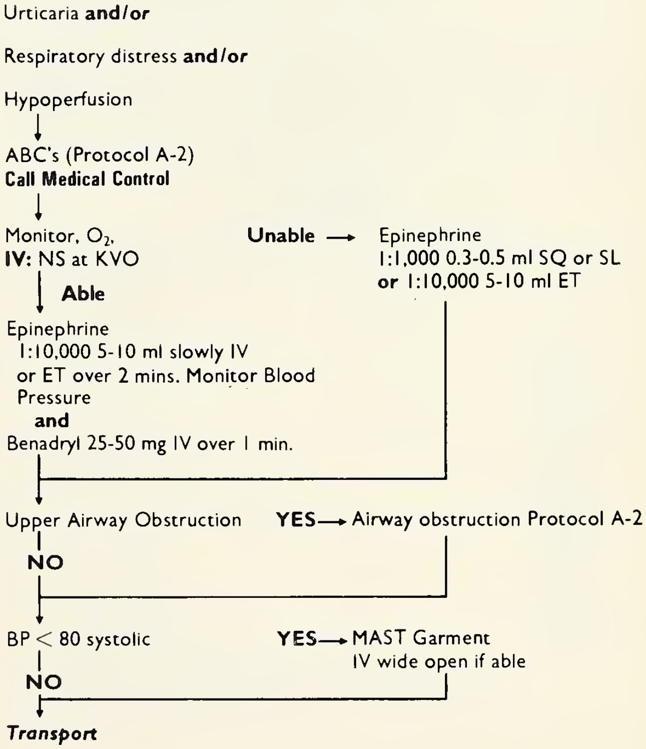
Treatment Protocol E-1
(Shock, Anaphylactic)

1. Recognize the patient with an acute systemic allergic reaction: wheezing, dyspnea, pruritis, facial edema, and hypotension/tachycardia (anaphylactic shock).
2. Open the airway and assist ventilation as outlined in Protocol A-2.
3. Begin O₂ by mask or nasal prongs at 6 L/min.
4. Monitor cardiac activity. Call Medical Control.
5. Place IV line. Begin NS at KVO rate.
6. Give epinephrine (5-10 cc of 1:10,000) IV slowly over two minutes.[a] Epinephrine may also be given endotracheally.
7. Give Benadryl 25-50 mg IV slowly over one minute; monitor BP.
8. Repeat step 6 at five-minute intervals as necessary. Consider use of MAST and fluid bolus.
9. Continue these supportive measures until transport is completed.

---

[a] For less severe reactions (urticaria without wheezing or hypotension) substitute Epinephrine (0.3 cc of 1:1,000) SQ. Repeat as necessary at 15-minute intervals.

ANAPHYLAXIS ALGORITHM


Urticaria **and/or**
Respiratory distress **and/or**
Hypoperfusion
ABC's (Protocol A-2)
Call Medical Control
Monitor, O₂,
IV: NS at KVO
Unable
Epinephrine 1:1,000 0.3-0.5 ml SQ or SL **or** 1:10,000 5-10 ml ET
Able
Epinephrine 1:10,000 5-10 ml slowly IV or ET over 2 mins. Monitor Blood Pressure
and
Benadryl 25-50 mg IV over 1 min.
Upper Airway Obstruction
YES
Airway obstruction Protocol A-2
NO
BP < 80 systolic
YES
MAST Garment IV wide open if able
NO
Transport

Treatment Pediatric Protocols A-1, A-1-0,
A-1-1, A-1-2, A-1-3, A-1-4, A-1-5, A-1-6,
A-1-7, A-1-8, A-1-9, A-1-10, A-1-11

Management Guidelines for Pediatric Patients

The following algorithms are based on current philosophies by pediatric emergency specialists and physicians who developed the Advanced Pediatric Life Support Course. Due to different circumstances and travel times for treatment, individualization is necessary in any management approach. All cases should be expeditiously transported to the designated emergency facility, avoiding any prolonged periods of time in the field. Appropriate equipment should be carried on all ambulances to properly care for the pediatric patient. The base station physician or paramedic may need to individualize therapy as per their regional protocols.

Intravenous Access

Establishment of an intravenous route in the pediatric patient can be difficult and time-consuming, especially if the child is in shock. Excessive time should not be spent in attempts to establish an intravenous route. When attempting to start an IV, the most easily accessible veins should be used, which include the antecubital fossa, saphenous vein in the ankle, or in rare circumstances, the external jugular vein. No more than five minutes should be used in attempting to establish this line. Normal saline or lactated Ringer's should be used for the pediatric patient.

The Pediatric Patient

D_5W should never be used on children in the field. Application of pediatric MAST trousers may assist in stabilization of fractures, decreasing bleeding from pelvic fractures, and possibly enhancing ability to start an intravenous line. The abdominal section may be inflated as long as the upper margin is below the 10th rib on the pediatric patient and there are no other contraindications to its use.

Oxygen

Oxygen administration should be given to any significantly injured or sick pediatric patient. Six liters per minute should be the flow for close-fitting mask, 12 to 15 liters per minute for mask with reservoir. Nasal cannulae or face mask should be used, based on which one is better tolerated by the child.

Table A-1-1
Estimated Pediatric Weight by Age

Age	Weight (kg)
Newborn	3.5
6 months	8
9 months	9
12 months	10
15 months	11
18 months	12
2 years	12.5
3 years	15
4 years	17
5 years	18.5
6 years	22
8 years	27
10 years	33
12 years	38

Wt (kg) ≈ (2 × age) + 8

Treatment Pediatric Protocol A-1
CPR — Basic

	Infant (≤1)	Young Child (1-8)
Compression		
Location	Mid Sternum	Mid Sternum
Depth	½ to ¾"	¾ to 1½"
Rate	100 per minute	80 per minute
Ventilation	1 breath per 5 compressions for all ages	

CPR — Advanced

Defibrillation 2 to 4 watt sec/kg

Endotracheal Tubes

	Wt (kg approx)	ET Tube (I.D.)	Suction Catheter
Newborn	<1	2.5-3.0	6 Fr
Newborn	>1	3.0-4.0	6- 8 Fr
6 mo	8	3.5-4.5	8 Fr
1 year	10	4.0-5.0	8-10 Fr
3 years	15	4.5-5.5	8-10 Fr
5 years	18.5	5.0-6.0	10 Fr
6 years	22	5.5-6.5	10 Fr
8 years	27	6.0-6.5	10 Fr
10 years	33	6.5-7.0	10 Fr
12 years	38	6.5-7.0	10 Fr
16 years	50	7.0-7.5	10 Fr

Table A-1-2
Medications

Drugs	Dosage
Epinephrine 1:10,000	0.1 cc/kg (10 mcg/kg)
NaHCO3 1 mEq/cc	1-2 cc/kg (1-2 mEq/kg)
Atropine 1 mg/cc	0.02 cc/kg (0.02 mg/kg)
Lidocaine 2%	0.05 cc/kg (1 mg/kg)
Calcium Chloride 10%	0.1 cc/kg (10 mg/kg)
$D_{25}W$	2 cc/kg (250 mg/cc)
Narcan	0.01-0.1 mg/kg

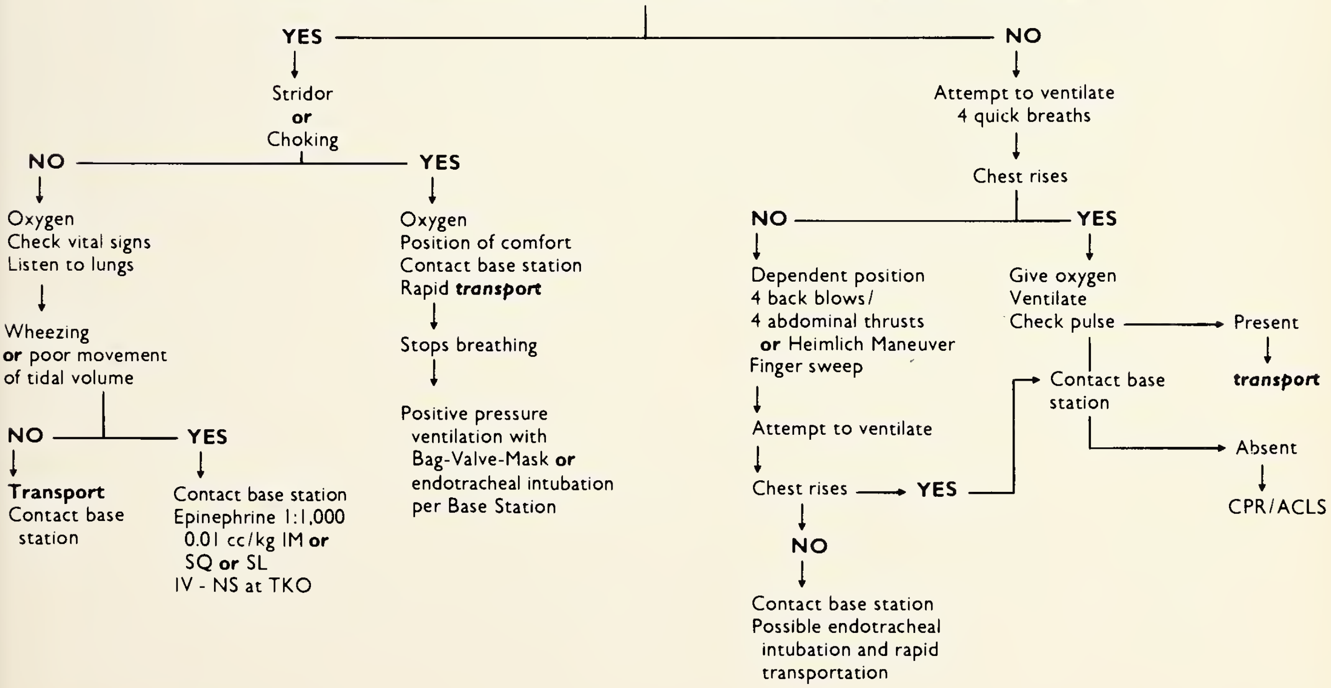
Infusion Drugs	Dosage
Dopamine 6 mg × Wt (kg) in 100 cc D_5W 1 cc/hr = 1 mcg/kg/min	5-20 mcg/kg/min
Lidocaine 2% 6 mg (0.3 cc) × Wt (kg) in 100 cc D_5W 1 cc/hr = 1 mcg/kg/min	10-40 mcg/kg/min
Isuprel 0.6 mg (3 cc) × Wt (kg) in 100 cc D_5W 1 cc/hr = 0.1 mcg/kg/min	0.1-0.5 mcg/kg/min
Epinephrine 0.6 mg (0.6 cc) × Wt (kg) in 100 cc D_5W 1 cc/hr = 0.1 mcg/kg/min	0.1-1.0 mcg/kg/min

Weights and Dosages

Parents may be able to relate to you the child's weight in pounds. If the parents do not know the child's weight, an estimate of the weight can be made, based on the child's age. Formula: weight in kilograms equals two times the age in years plus eight. In addition, tables can be referenced for approximate weights, based on the patient's age. All medications can then be calculated on a dose per kilogram basis. Routes available in the pediatric patient include intravenous, intramuscular, subcutaneous, and sublingual.

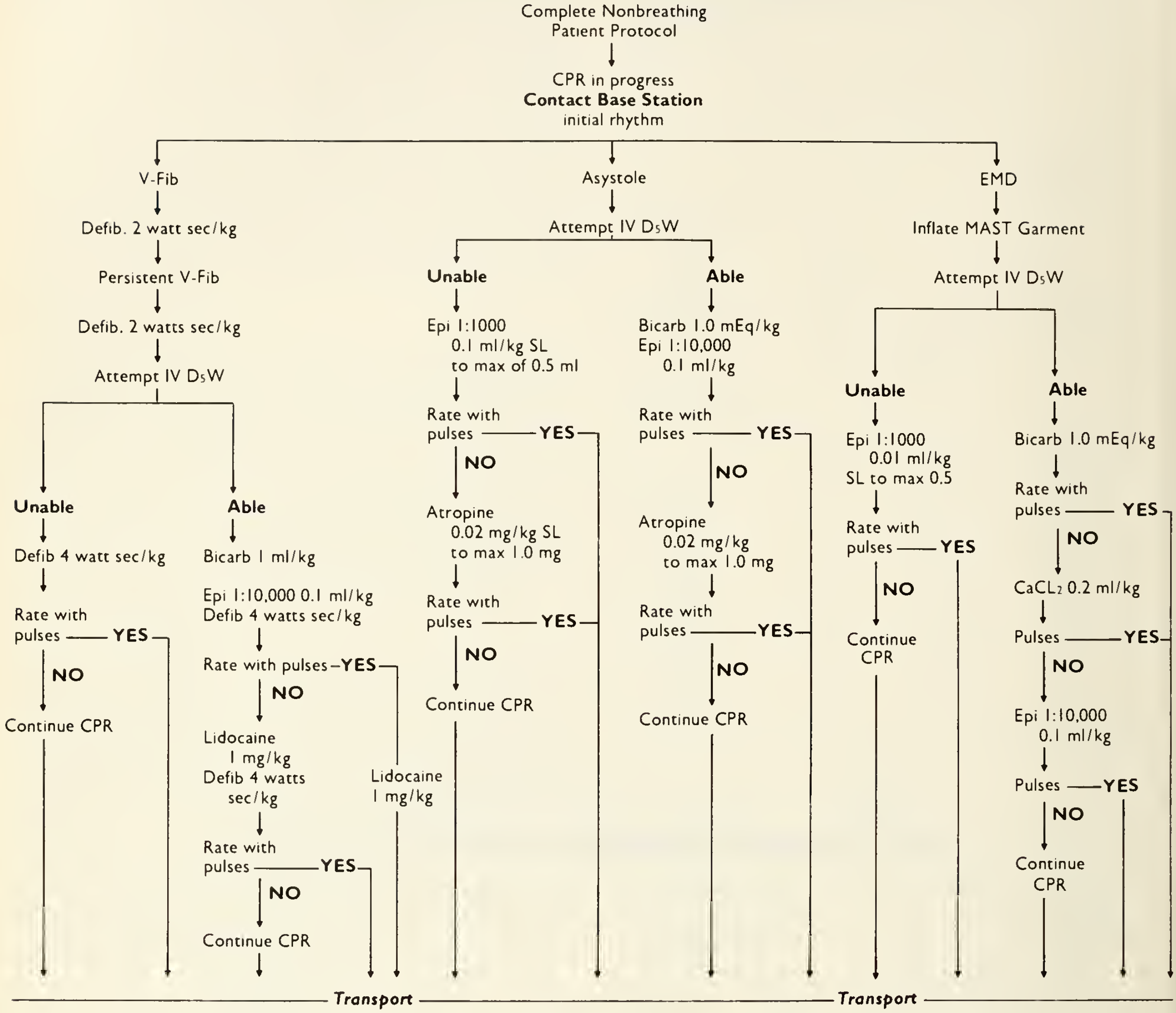
Treatment Pediatric Protocol A-1-0

ABSENT RESPIRATIONS AND AIRWAY OBSTRUCTION



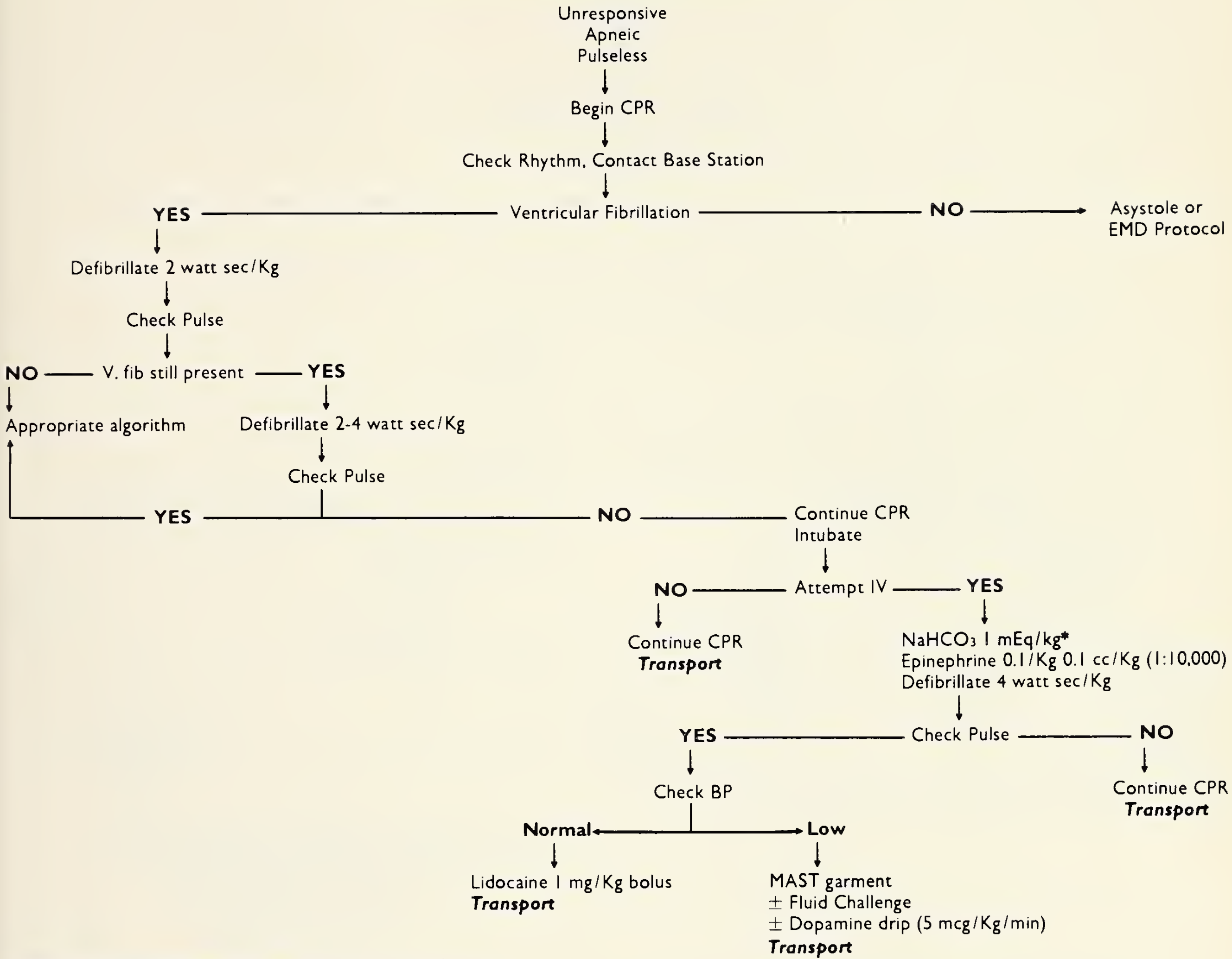
Treatment Pediatric Protocol A-1-1

PULSELESS, NONBREATHING PATIENT



Treatment Pediatric Protocol A-1-2

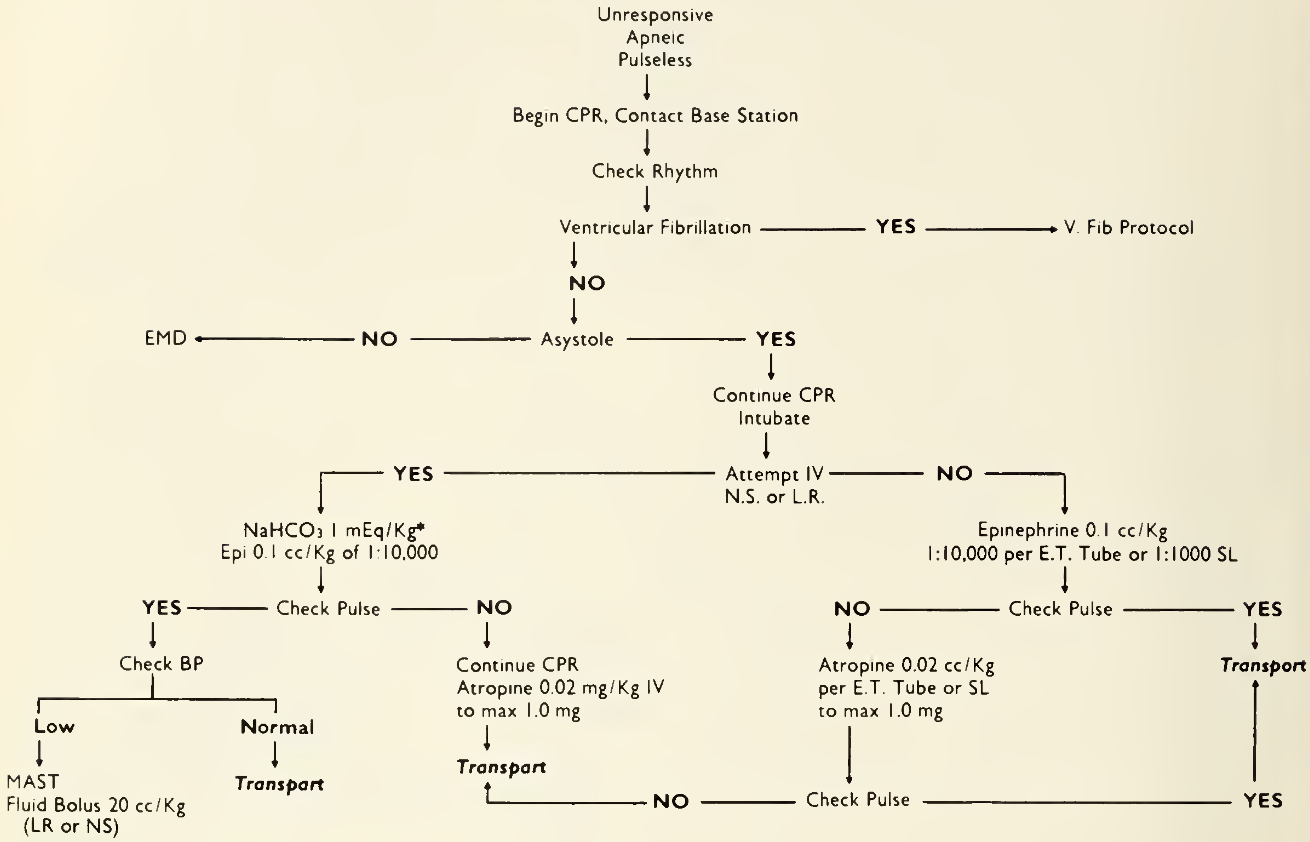
VENTRICULAR FIBRILLATION



*Dilute c̄ equal volume sterile water if under 6 mos. of age

Treatment Pediatric Protocol A-1-3

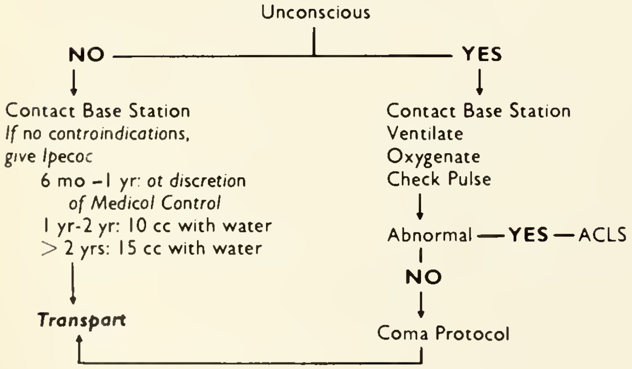
ASYSTOLE



*Dilute c̄ equal volume sterile water if under 6 mos. of age

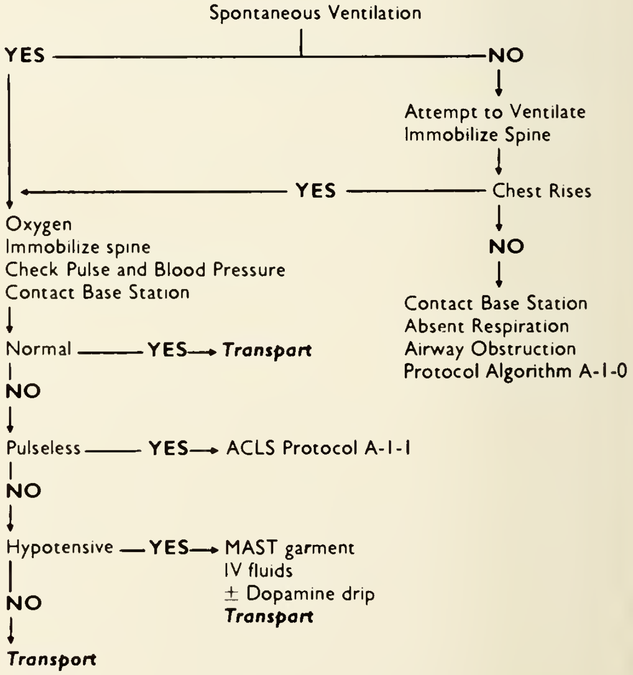
Treatment Pediatric Protocol A-1-4

INGESTION



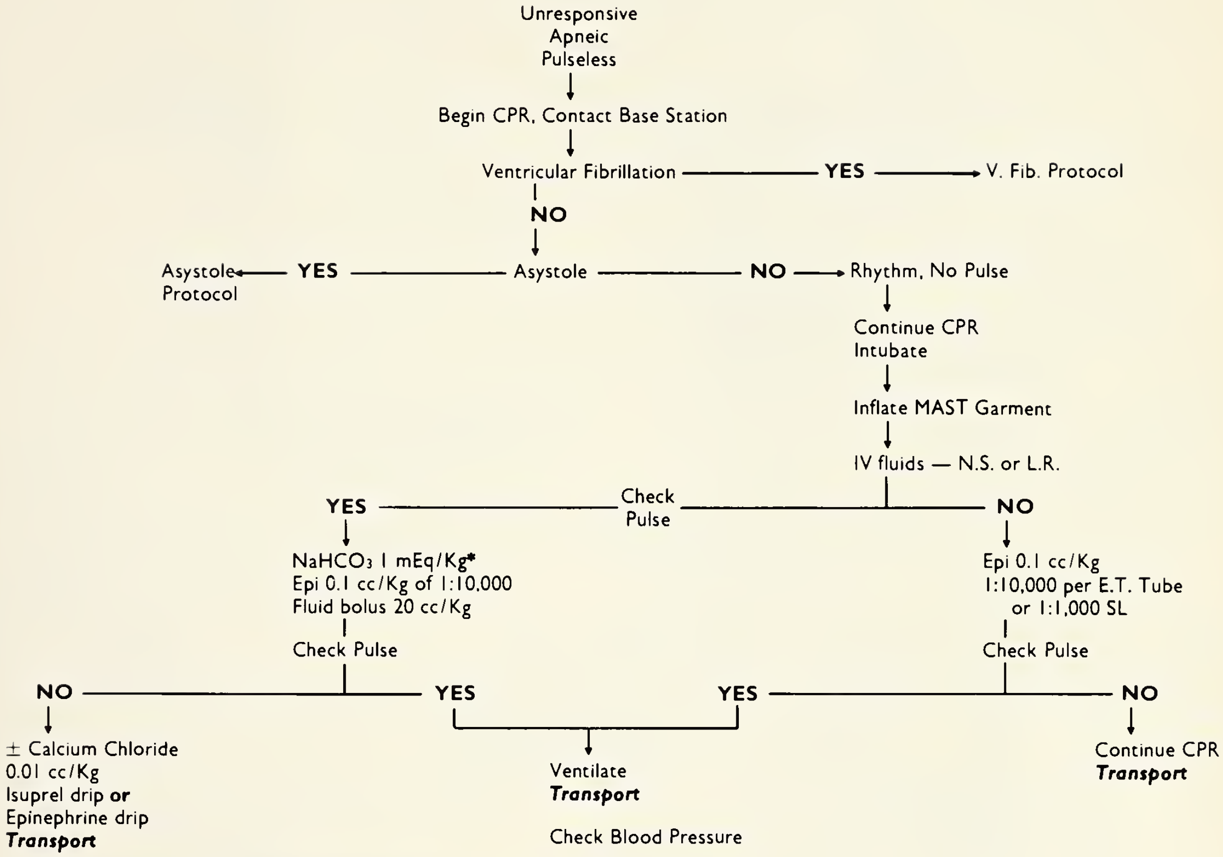
Treatment Pediatric Protocol A-1-5

NEAR DROWNING



Treatment Pediatric Protocol A-1-6

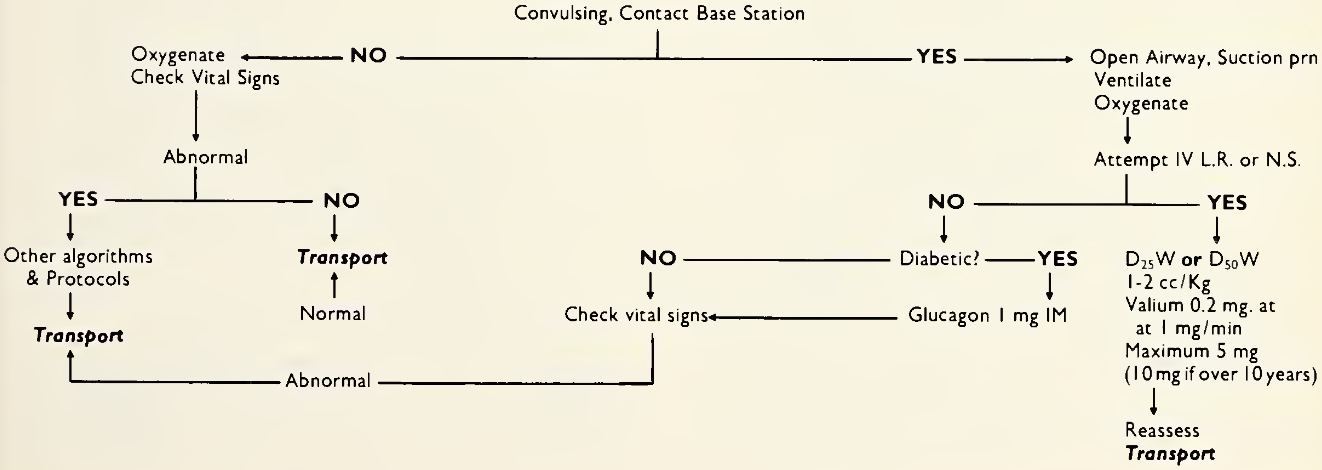
EMD



*Dilute c̄ equal volume sterile water if under 6 mos. of age

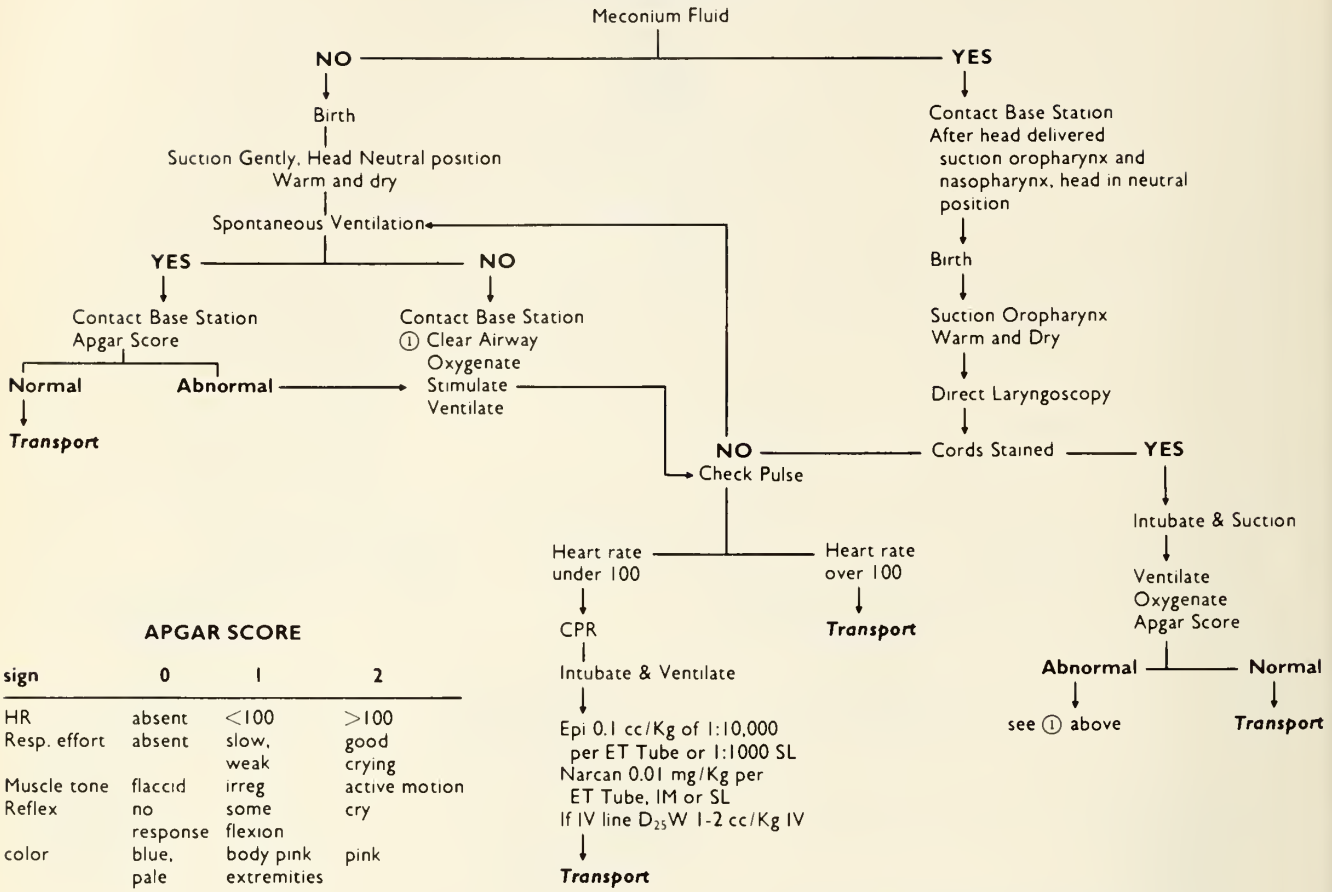
Treatment Pediatric Protocol A-1-7

SEIZURES



Treatment Pediatric Protocol A-1-8

NEONATAL RESUSCITATION



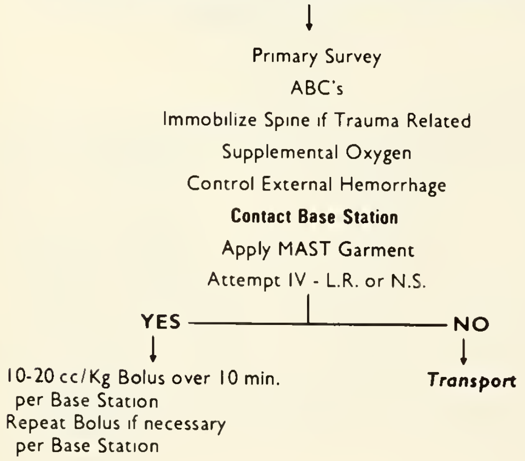
APGAR SCORE

sign	0	1	2
HR	absent	<100	>100
Resp. effort	absent	slow, weak	good crying
Muscle tone	flaccid	irreg	active motion
Reflex	no response	some flexion	cry
color	blue, pale	body pink extremities blue	pink

Treatment Pediatric Protocol A-1-9

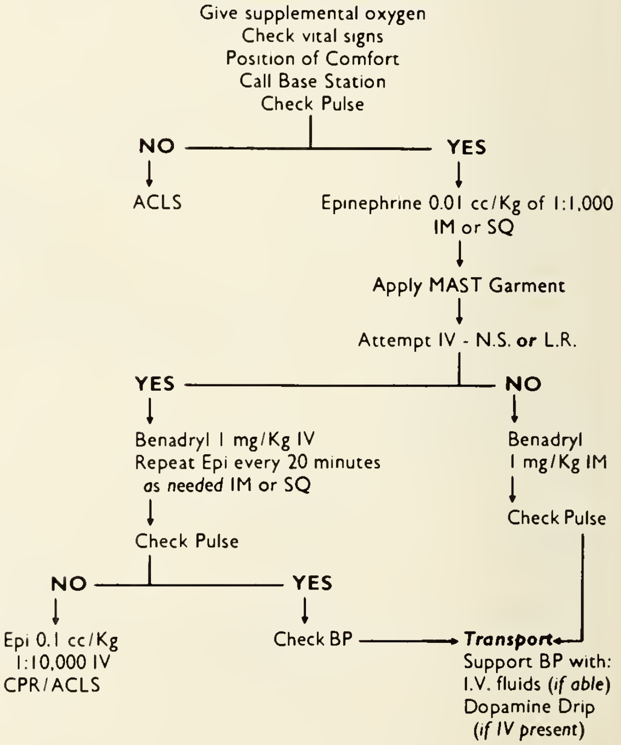
HYPOVOLEMIC SHOCK

(Dehydration, burn, hemorrhage, trauma)


Primary Survey
ABC's
Immobilize Spine if Trauma Related
Supplemental Oxygen
Control External Hemorrhage
Contact Base Station
Apply MAST Garment
Attempt IV - L.R. or N.S.
YES
10-20 cc/Kg Bolus over 10 min.
per Base Station
Repeat Bolus if necessary
per Base Station
NO
Transport

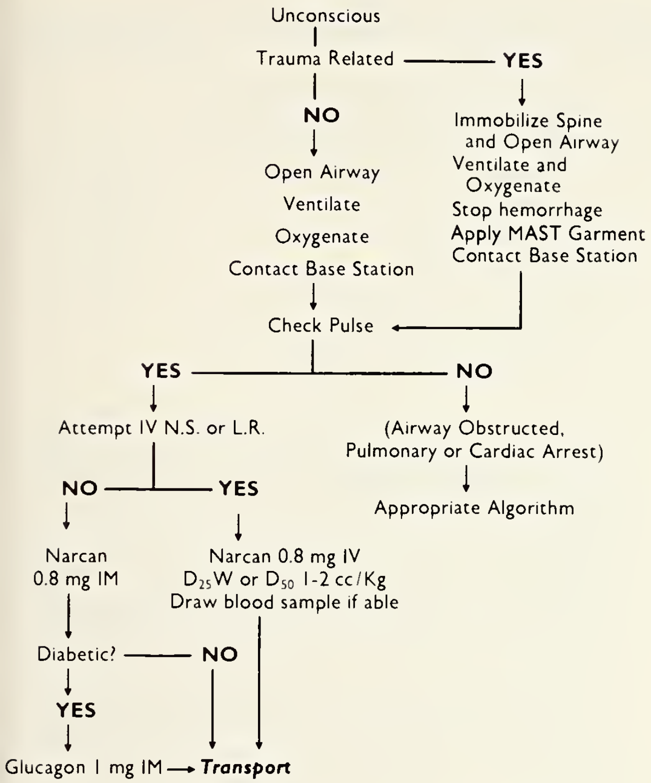
Treatment Pediatric Protocol A-1-10

ANAPHYLAXIS



Treatment Pediatric Protocol A-1-11

COMA



Treatment Protocol, General F-1
(Eye Trauma)

The patient may present with eye trauma alone or other facial injuries. Injuries may be penetrating, blunt and/or chemical in nature. Injury may be obvious, i.e., a foreign body extruding from the eye. Injury may be more subtle, i.e., eye red or watering, or a small puncture to globe with cloudiness of or blood in anterior chamber (hyphema).

I. See S.O.P. for general assessment
II. Initial emergency care*
  1. Establish and maintain airway with oxygen and assure adequate ventilation. Have patient sit up at 45° angle. Keep patient quiet and comfortable if possible.
  2. Do not apply pressure to suspected penetrating eye injury in an attempt to examine the eye.
  3. Apply a loose metal shield to injured eye.
  4. If the injury involves a chemical burn, immediately irrigate with 2 liters of saline or water solution after instilling Tetracaine 1 drop.
  5. Bring a sample of the agent causing the injury when possible.
  6. Connect to monitor.
III. Establish communications with Medical Control base station as necessary
IV. Definitive care by physician order via voice communications as necessary
  1. Continue to monitor and transport to appropriate facility all severe penetrating eye injuries, severe injuries to eyelids, severe trauma to eye and chemical burns to eye.

Treatment Protocol, General F-2
(Seizures)

I. See S.O.P. for general assessment
II. Initial emergency care
  1. Establish and maintain airway with oxygen and *assure adequate ventilation.*
  2. CPR as necessary.
  3. Establish IV as necessary with NS @ KVO rate.
  4. Dextrose 50 cc 50% IV push.
  5. Loosen clothing.
  6. Insert bite block if possible.
  7. Observe characteristics of seizure.
  8. Provide patient safety.
  9. Seizures may be a result of a toxic exposure or trauma. Look around patient for evidence of chemical exposure — i.e., containers, vials or objects that may have injured patient.
III. Establish communications with Medical Control base station as necessary.
  1. Transmit EKG.
IV. Definitive care by physician order via voice communications as necessary
  1. Continue to monitor and transport.

Treatment Protocol, General F-3
(Psychiatric)

I. See S.O.P. for general assessment
  Sudden appearance of unusual, disordered or socially inappropriate behavior.
  Specific observation for:
    Signs of physical illness or trauma
    Physical environment
    Social environment
    Medical/psychiatric history
    Medications/abused substances
    Extreme hostility, violence or suicidal behavior
II. Initial emergency care*
  1. Reassurance of patient
  2. Reassurance of family/friends
  3. Thorough explanation to patient and family of all procedures
  4. If patient appears dangerous notify police and await assistance
  5. Treat trauma per protocol D-O as appropriate
  6. Possible organic disorder
    Establish IV line D_5W at KVO. Draw red top tube and administer $D_{50}W$ 50 cc IV
  7. Transport
  8. Appropriate physical restraints as per Medical Control
III. Establish communications with Medical Control base station as necessary
  1. Transmit EKG
IV. Definitive care by physician order via voice communications as necessary

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* For partial and complete ocular enucleations apply sterile wet saline dressing.

1. Continue to monitor and transport

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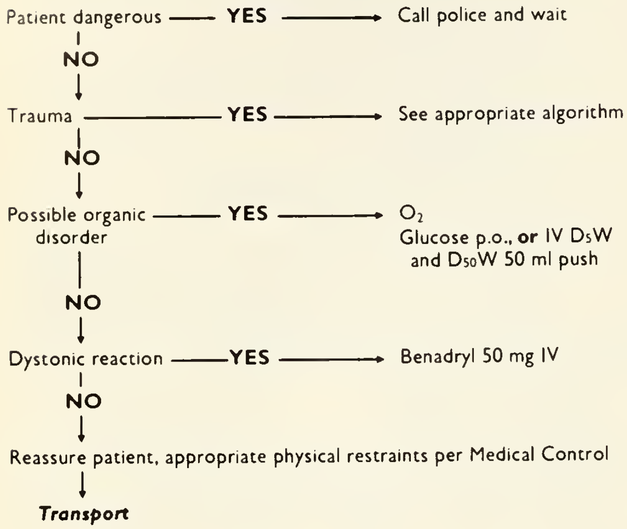
* The assistance of the police department may be required in the case of extremely violent, combative patients, especially when homicidal/suicidal intent seems apparent.

BEHAVIOR DISORDER ALGORITHM


Patient dangerous
YES
Call police and wait
NO
Trauma
YES
See appropriate algorithm
NO
Possible organic disorder
YES
O_2
Glucose p.o., or IV D_5W and $D_{50}W$ 50 ml push
NO
Dystonic reaction
YES
Benadryl 50 mg IV
NO
Reassure patient, appropriate physical restraints per Medical Control
Transport

Treatment Protocol, General F-4
(Heat Exposure)

I. See S.O.P. for general assessment
II. Initial emergency care
  1. Establish and maintain airway with oxygen and assure adequate ventilation.
  2. CPR as necessary.
  3. Establish IV as necessary with NSS @ KVO rate.
  4. Move to cool, well-ventilated location; loosen or remove clothing.
  5. Cool body.
III. Establish communications with Medical Control base station as necessary
  1. Transmit EKG
IV. Definitive care by physician order via voice communications as necessary
  1. IV rate to be determined at discretion of physician.
  2. Continue to monitor and transport.

Treatment Protocol, General F-5
(Hypothermia)

I. See S.O.P. for general assessment
  Specific observations for:
    Altered levels of consciousness
    Lowered body temperature
    Exposed environment
    Special attention to elderly patient
II. Initial emergency care*
  1. Establish and maintain airway and assure adequate ventilation
  2. Administer low flow oxygen
  3. Apply electrodes and monitor EKG
  4. Start IV of D_5W @ KVO rate
  5. Transport immediately
III. Establish communications with Medical Control base station as necessary
  1. Transmit EKG
IV. Definitive care by physician order via voice communications as necessary
  1. Continue to monitor and transport

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* Precautions — Hypothermia patients tend to have a very unstable cardiac condition. To reduce the possibility of dysrhythmias, especially ventricular fibrillation, the following precautions are advised:
1. Avoid use of EOA or ET tubes.
2. Avoid over-ventilating.
3. Check very carefully for heart beat as CPR can cause ventricular fibrillation.
4. Move patient as little as possible. Handle patient with great care.
5. Morphine, Atropine, Isuprel and Epinephrine are contraindicated. Lidocaine may be used.
6. Clothing should be removed in the Emergency Department.
7. No attempts should be made to warm the patient during pre-hospital care or transport. The temperature of the patient compartment should approximate the patient's body temperature.
8. Defibrillation is generally *not* successful in patients with low core temperature.

Treatment Protocol, General F-6
(Frostbite)

I. See S.O.P. for general assessment
II. Initial emergency care
  1. Establish and maintain airway with oxygen and assure adequate ventilation.
  2. Establish IV as necessary with D_5W @ KVO rate.
  3. Gently remove any clothing from affected area.
  4. If an extremity is affected, gently separate fingers or toes by placing sterile cotton between them and apply dry sterile dressing.
  5. Cover frostbitten ears or nose with a warm hand.
  6. Splint and control bleeding as necessary.
  7. Do *not* rub skin.
  8. Do not permit the patient to smoke as nicotine will constrict the arteries and thereby further compromise blood flow to the affected part.
  9. Do not apply pressure or constrict.
III. Establish communications with Medical Control base station as necessary
  1. Transmit EKG
IV. Definitive care by physician order via voice communications as necessary
  1. Continue to monitor and transport.

Country Doctoring in North Carolina Dr. J. H. Ellington and Changing Times

Paul I. Crellin

> *Please come and see my wife. She is in a bad condition. She is nearly in the fit that Bill Ward's wife was and I want you to come just as soon as you get this and see her. And I will pay you for your visit. If you can't wait till I sell my tobacco I will pay you in corn as soon as I can gather my corn. Please come at once.*

DR. James H. Ellington (1850-1929) responded to countless such undated requests during his fifty-seven years of rural practice from 1872 until his death in 1929. Practicing in and around Sandy Ridge, which lies in a sparsely populated part of Stokes county near the Virginia border, during a time of rapid change in medicine, he established an enviable local reputation. Nowadays the "old-time" country doctor tends to evoke a great deal of nostalgia, even though little is known about the life and practices of most of them. James Ellington is different. While he left no printed record of his attitudes and approaches toward medicine, his papers, letters, student lectures notes, ephemera, books and artifacts have survived, many still in the trunk he had as a medical student from 1870 to 1872. Even his white frame, single-room office remains as it was on the grounds of his large house and farm (figure 1). Inside, as of early 1985, amid fifty years of dust and dirt, are remains of his practice: bottles of medicine, books, calendars, journals, and a profusion of medical instruments, including a scarificator for bloodletting.

Ellington's medical education in the late 1860s and early 1870s was typical of the time: an apprenticeship, of which no details have been found, followed by two five-month sessions at medical school. On September 14, 1870, Ellington received a letter of acceptance from the Washington University School of Medicine in Baltimore informing him that he was admitted with a scholarship to the next course of lectures beginning on October 1. Information about the curriculum shows that it provided a solid education with emphasis on clinical medicine. Ellington's own notes suggest that he was taught to critically assess existing medical practices and not to cling to established diagnoses and treatments.

Ellington's education prepared him to keep abreast of the many changes that took place in medicine during the next fifty years. His continuing contacts with colleagues and purchases of textbooks and journals suggest conscious efforts to keep up-to-date. Although he did not attend the annual meetings of the North Carolina Medical Society, he was active in the Stokes County Medical Society, serving at times as president.

Also important in alerting him to developments — at least within therapy — was the considerable quantity of advertising mail he received from pharmaceutical companies. He kept much of it, suggesting that he hardly treated it as junk mail. Companies like Parke, Davis bombarded him in the 1890s with details of new treatments, many of them linked to the newly established germ theory: for instance, intestinal disinfection treatment for typhoid, which included the Woodbridge method. This was a complex regimen involving a mixture of capsules and tablets containing podophyllum, calomel, guaiacol carbonate, menthol and eucalyptol. In 1899, another company, Viskolein, reminded Ellington of their own typhoid treatment, which was probably similar to that of Parke, Davis. Viskolein gave no information on ingredients, only a fanfare of physicians' testimonials.

Another prominent therapeutic approach was serum therapy along with new and improved vaccines. The Mulford Company introduced the physician's "mailcard," sent out (c.1905) by druggists advertising, for example, Mulford's Glycerinized Vaccine Lymph and "points" for inoculation. "The laboratory," the card stated, "in which this vaccine is produced is the most complete in existence and is under the direction of practical and specially trained bacteriologists."

Ellington practiced through a time of growing commercialism within medicine both in the office and for home treatment. On the back of one note he received from a patient is an almanac advertisement for "Dr. Sage's Catarrh Cure." Ellington himself used physicians' day books supplied by the Pierce Medicine Co., one of the successful entrepreneurs of the day, and sold proprietary products, including Pierce's, from his office-pharmacy (figure 2).

Unfortunately, Ellington's records, full of family matters and business arrangements, do not indicate whether his clinical skills changed during fifty years of practice. Certainly he never undertook much surgery, probably only performing minor procedures like suturing cuts and remov-

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From the Country Doctor Museum, Bailey 27807.

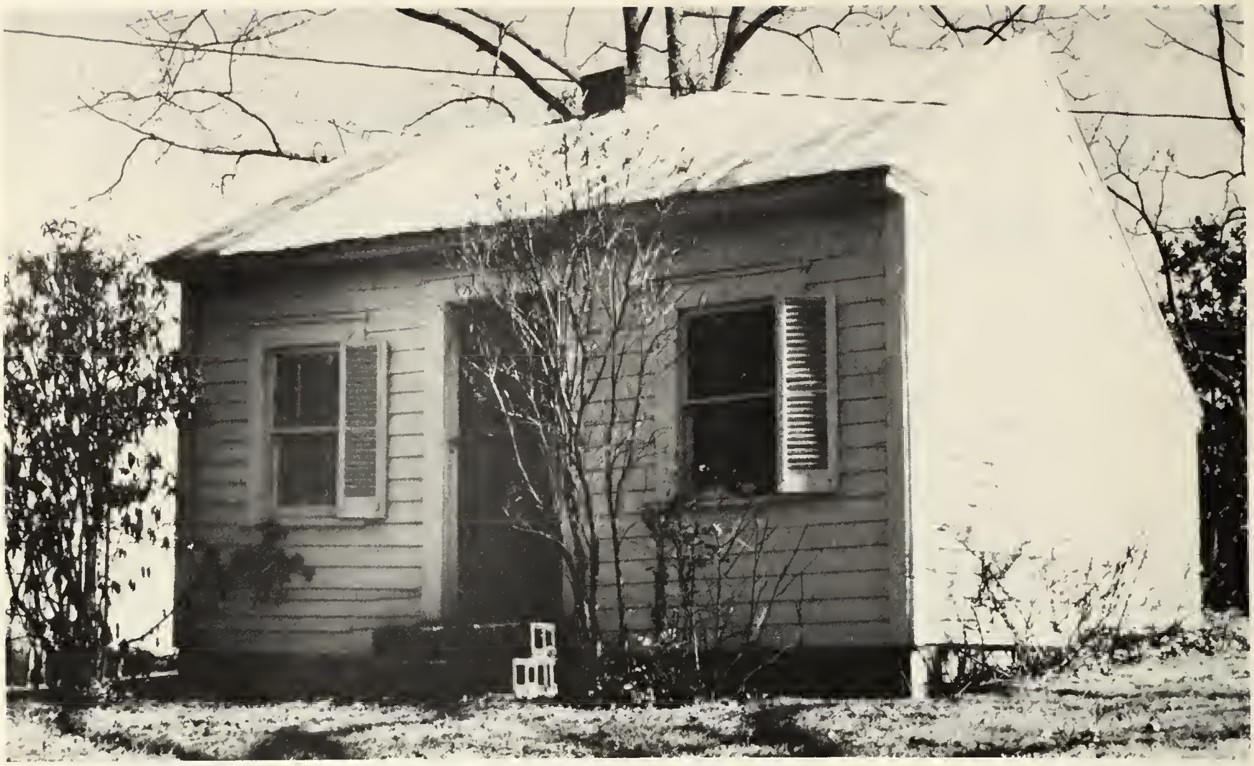

Figure 1. *Dr. J. H. Ellington's one-room office. Photo taken in January 1985.*

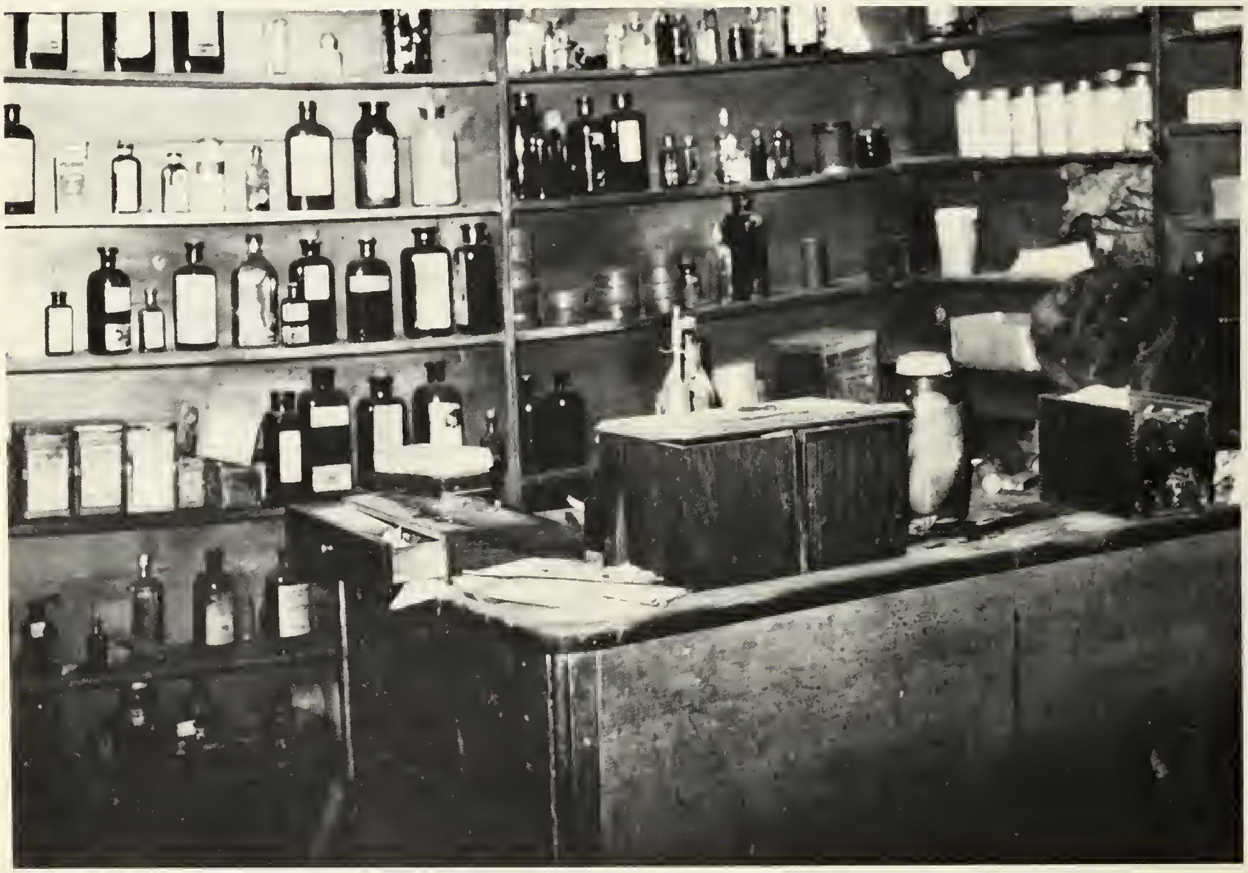

Figure 2. *Interior of the office, showing medicine bottles and counter (January 1985).*

ing buckshot. Rather than performing "kitchen table" surgery as described in Nicholas Senn's *Practical Surgery for the General Practitioner* (Philadelphia, 1901), he referred patients to Drs. Wesley Long and Reeves of Greensboro.

No diagnostic aids like a microscope (to examine urine deposits and sputum for tuberculosis organisms) or sphygmomanometers have been found in the office; on the other hand, records of his stock of medicines, a few surviving prescriptions and the numerous bottles in the office suggest a sense of eclecticism and a willingness to try new remedies. His notes record many polypharmaceutical preparations, then declining in popularity. One was a "tonic cholagogue" containing quinine sulphate, extract of leptandrin, tincture of stillingia, extract of podophyllin, oil of sassafras, oil of gaultheria all in cinnamon water.

Ellington purchased his medicines from such local companies as the Richardson Drug Co. of Greensboro, famed for the manufacture of Vick's products, and from major pharmaceutical companies like Massengill of Tennessee. From the latter he bought large quantities of one of the most interesting of medicines, the obnoxious, garlicky-smelling asafetida. However, he bought it as "tasteless" pills and probably employed it as a mild sedative for "nervous complaints" and as a general antispasmodic. Much of its local popularity was probably linked with its reputation among many Southerners as a cure-all. Children often hung a small lump in a sack around the neck.

Ellington's considerable range of medicines certainly allowed him to tailor prescriptions to the whims of patients. Judging from the number of housecalls he made — averaging three to four a day for long periods — he probably knew his patients well. Personal consideration for patients is considered one of the hallmarks of country doctors, implying, often unfairly, that other attributes such as clinical skills in diagnosis and therapy were commonly behind the times. While the richness of Ellington's surviving personalia is frustratingly bare of clinical details about his practice, it suggests that his reputation rested on more than good bedside manners.

From all the available evidence, comments made in 1912 about Ellington the man may reflect the attitudes of Ellington the physician concerned with keeping up with medical progress during the progressive era: "Dr. Ellington has been, and is yet, one of our most valuable assets to citizenship. He has seen the dawn of a better day in our country. For this condition he has worked faithfully for many years. Nothing daunts him yet when it comes to public-spirited work. He is just as eager to see our country progress as he ever was, and lends his influence in that direction. Constructive in his views and progressive in his acts, he is an invaluable man, doing his fellows an unspeakable amount of good."

Acknowledgment

I wish to thank Mr. John Ellington and Mrs. Maggie Ellington for generous access to the Ellington manuscripts and artifacts. Mrs. Ellington's hospitality added much to capturing the ethos of country doctoring in Sandy Ridge. Access to the material was facilitated by accession list prepared by Dr. David Hall when a medical student at Duke University.

*Biographical note: The library of the Country Doctor Museum has a policy of collecting the scattered autobiography and biography of Country Doctors.

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Each tablet contains aspirin (acetylsalicylic acid) 325 mg plus codeine phosphate* Ⓒ III
in one of the following strengths: No. 2—15 mg, No. 3—30 mg, and No. 4—60 mg.
(*Warning—may be habit-forming.)

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Before prescribing, please consult complete product information, a summary of which follows.

EMPIRIN® with Codeine Tablets C-III

DESCRIPTION: Contains aspirin 325 mg and codeine phosphate*: No. 2 — 15 mg, No. 3 — 30 mg, No. 4 — 60 mg. *WARNING: May be habit-forming. Empirin with Codeine has analgesic, antipyretic and anti-inflammatory effects.

CONTRAINDICATIONS: (1) Hypersensitivity or intolerance to aspirin or codeine; (2) severe bleeding, disorders of coagulation or primary hemostasis, including: hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenias, thrombasthenia, other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency, severe liver damage; (3) anticoagulant therapy; (4) peptic ulcer or other serious gastrointestinal lesions.

WARNINGS: Therapeutic aspirin doses can cause: anaphylactic shock, other severe allergic reactions. History of allergy is often lacking. Preoperative aspirin may prolong bleeding time. Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders. With head injury or other intracranial lesions, the respiratory depressant effects of narcotics, as well as their capacity for elevating CSF pressure, may be markedly enhanced. Narcotic-produced drowsiness or other CNS depressant effects may further obscure clinical course of patients with head injuries. Narcotics may obscure diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS: General: Prescribe cautiously for the elderly or debilitated; patients with severe renal or hepatic function impairment, gallbladder disease, gallstones, respiratory impairment, cardiac arrhythmias, inflammatory GI disorders, hypothyroidism, Addison's disease, prostatic hypertrophy, urethral stricture, coagulation disorders, head injuries, acute abdominal conditions. Should not be prescribed long-term unless specifically indicated. Take precautions when administering salicylates to persons with known allergies. Aspirin hypersensitivity is particularly likely in patients with nasal polyps and relatively common in asthmatics. **Drug Interactions:** Empirin with Codeine may *enhance* effects of: MAO inhibitors, oral anticoagulants, oral antidiabetic agents, insulin, 6-mercaptopurine, methotrexate, penicillins, sulfonamides, non-steroidal anti-inflammatory agents, narcotic analgesics, alcohol, general anesthetics, tranquilizers (e.g., chlordiazepoxide), sedative-hypnotics, other CNS depressants, corticosteroids. Empirin with Codeine may *diminish* effects of: uricosurics (e.g., probenecid, sulfinpyrazone). Para-aminosalicylic acid, furosemide, vitamin C may cause aspirin and its metabolites to accumulate, perhaps to toxic levels. **Pregnancy:** *Teratogenic Effects:* Pregnancy Category C. No animal reproduction studies have been conducted. It is not known whether Empirin with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Give to a pregnant woman only if clearly needed. Rabbit and rat reproduction studies at up to 150 times human dose revealed no evidence of impaired fertility or harm to fetus due to codeine. *Nonteratogenic Effects:* Therapeutic aspirin doses in pregnant woman close to term may cause bleeding in mother, fetus or neonate. During last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery. **Labor and Delivery:** Aspirin ingestion prior to delivery may prolong delivery or lead to bleeding in mother or neonate. Codeine use during labor may lead to respiratory depression in neonate. **Nursing Mothers:** Aspirin and codeine are excreted in breast milk in small amounts, but significance of effects on nursing infants is not known. Because of potentially serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to mother.

ADVERSE REACTIONS: Codeine: Most frequent: lightheadedness, dizziness, drowsiness, nausea, vomiting, constipation, respiratory depression. Less common: euphoria, dysphoria, pruritus, skin rashes. **Aspirin:** Chronic use of large doses may result in salicylism. Manifestations: nausea, vomiting, hearing impairment, tinnitus, diminished vision, headache, dizziness, drowsiness, mental confusion, hyperpnea, hyperventilation, tachycardia, sweating, thirst. Therapeutic doses can induce mild or severe allergic reactions which may be manifested by: skin rash, urticaria, angioedema, rhinorrhea, asthma, abdominal pain, nausea, vomiting or anaphylactic shock. Some patients cannot take aspirin or other salicylates without developing nausea or vomiting. Occasional patients respond to aspirin (usually in large dose) with dyspepsia or heartburn (may be accompanied by occult bleeding). Excessive bruising or bleeding sometimes seen in patients with mild primary hemostasis disorders who regularly use low doses of aspirin. Prolonged use can cause painless erosion of gastric mucosa, occult bleeding and infrequently, iron-deficiency anemia. High doses can exacerbate peptic ulcer symptoms and, occasionally, cause extensive bleeding. Excessive bleeding can follow injury or surgery in patients with or without known bleeding disorders who have taken therapeutic aspirin doses within preceding 10 days. Hepatotoxicity has been reported in association with prolonged use of large aspirin doses in lupus erythematosus, rheumatoid arthritis and rheumatic disease patients. Bone marrow depression (manifestations: weakness, fatigue, abnormal bruising, bleeding) has occasionally been reported. In patients with glucose-6-phosphate dehydrogenase deficiency, aspirin can cause a mild degree of hemolytic anemia. In hyperuricemic persons, low aspirin doses may reduce effectiveness of uricosurics or precipitate a gout attack.

DOSAGE AND ADMINISTRATION: Adjust dosage according to pain severity and patient's response. It may occasionally be necessary to exceed usual recommended dosage when pain is severe or patient has become tolerant to codeine's analgesic effect. Empirin with Codeine is given orally. Usual adult dose: Empirin with Codeine No. 2 or No. 3: 1 or 2 tablets every 4 hours as required. Empirin with Codeine No. 4: 1 tablet every 4 hours as required. Tablets should be taken with food or full glass of milk or water to lessen gastric irritation.

Wellcome

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Research Triangle Park
North Carolina 27709

The Do's and Don'ts of Responsible PA Practice

James E. Hill, Jr., P.A.-C., M.Ed.

- *The physician/physician assistant team requires dotted i's, crossed t's and careful attention to detail. See the accompanying editorial by F. Maxton Mauney, Jr., M.D. on page 609.*

"AIDING and abetting the illegal practice of medicine." That's a frightening statement to hear, particularly if you're a physician and the statement is made by the North Carolina Board of Medical Examiners (BME). Unfortunately, the rare physicians guilty of such an act may be in trouble, not because of purposely setting out to break the law, but because of having utilized their PAs without carefully checking the rules. The PAs involved in a situation like this should have known better. Common sense should dictate to them the incorrectness of certain everyday practice patterns. Unfortunately, common sense is not always common.

Here is an example of how the reality of practice can cause both physician and PA to make mistakes:

M.D.: "I'm going to Pinehurst for our annual conference so I can attend some lectures and meetings which will make me a better physician. Dr. X, who normally supervises you when I'm out of town, is going, too, so Dr. Y will be available to back you up if any problems arise in the practice."

P.A.: "But, sir, Dr. Y is not listed with the Board of Medical Examiners as a back-up supervising physician for me."

M.D.: "Also, in case you need to write a controlled substance prescription for any of our patients while I'm gone, I'm leaving you a few presigned prescriptions."

P.A.: "But, sir, presigned prescriptions are against the Board's policy and are likely to get us both in big trouble."

M.D.: "When I get back, there will be a nice bonus for you since you're doing this extra work for me and our patients."

P.A.: "I don't like this but you're the boss. Have a good trip."

At a spring meeting in Pinehurst between the Board of Medical Examiners and representatives of the North Carolina Academy of Physician Assistants and some of the North Carolina Physicians Assistants' advisors, the BME members expressed their concerns about common and repetitive problems in physician/PA practices. This paper presents those problems in a "Do's and Don'ts" format so that all of us will be clearer about an ideal practice and the pitfalls of shortcuts in proper PA supervision. We hope the BME investigators will have much less to report and those physicians who unwittingly utilize PAs inappropriately will be forewarned.

The "Don'ts"

1) Don't forget to notify the BME if there are deletions or additions to the supervising physician registration list or if the PA is carrying out functions not listed in the original PA application or in the most recent registration. These are simple tasks. They cost no money. And yet, many practices overlook the importance of updating with the Board of Medical Examiners the list of physicians responsible for the PA. This problem shouldn't exist since PAs function only under the license of a physician and, more specifically, only under the license of a physician registered with the BME as supervising physician for that PA.

2) Don't give anyone, including your PA, a presigned prescription blank. Presigned prescription blanks are a convenient way for physicians to allow their PAs to write excluded drugs (i.e., controlled substances) for patients without the trouble of signing each prescription as the need arises. It's usually justified by saying that the relationship is stable enough for the PA to be trusted (with judgment and discretion) to write only previously agreed upon drugs and in previously agreed upon situations. This practice has its own inherent risks. The presigned prescription blanks can be mislaid or stolen and can then be used by those with sociopathic tendencies for the carte blanche privilege of writing their favorite mind or mood altering drug. That's a risk no physician or PA should take and it can be prevented simply by having the PA fill out a prescription for a needed controlled substance, sign it, and then have the physician sign it *after reviewing the need*. The PA's signature lets the pharmacist know that the physician and PA collaborated in writing the prescription.

3) Don't let your PA write a prescription for medications that are specifically excluded on the Formulary. Another area of question concerning prescriptions deals with excluded drugs other than controlled substances and with the issue of refills. A PA cannot write for an excluded drug (like Coumadin or Vistaril) and cannot authorize refills on a prescription *except* when he writes for that drug or authorizes refills *on the order of the supervising physician*. The supervising physician need not sign the prescription in these cases but the letter of the law requires the physician to verbally authorize the drug or refill each time it's given. It

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From the Department of Emergency Medicine, Charlotte Memorial Hospital, 1000 Blythe Boulevard, Charlotte 28234.

cannot be a standing order and the PA must write the prescription as a "verbal order of" the physician. For example, the signature area would look like this: "J. Hill, P.A.-C. per verbal order of J. Baker, M.D." Of course, this procedure *cannot* be done for controlled substances since they require a physician's signature.

4) Don't permit your PA employee to replace you as a supervising physician for PA students from Duke University Medical Center or Bowman Gray School of Medicine. Both have excellent programs and both programs use physicians in private practice across the state as preceptorships for the clinical phase of training. Some of these practices already have graduate PAs working in them. The BME has discovered that sometimes the graduate PA is primary supervisor of the PA student. The physician employer sees only the complicated cases of the student. Just as the decision to add a graduate PA to the staff must be made with the best interests of the patient and practice in mind, the decision to add PA students to the practice setting must be made only if the physician has the time and interest to adequately supervise the student's activities. This is not to say that a graduate PA in the practice cannot be used as a role model for a student, allowing him to witness the real world of a physician/PA team at work.

5) Don't allow your PA to sign prescriptions for PA students or medical students. The author has been actively involved as an officer or committee chairman in our state's professional academy since 1977 and has worked as a PA in this state's largest emergency department since 1976. Those of us who met with the BME this spring thought that we had seen and heard it all but the Board reported to us an activity that surprised me. It seems that an occasional PA graduate working with PA students provided them with prescriptions for commonly used antibiotics and other medicines. They ignored the requirement that each prescription has to be signed at the time the patient is seen. This is a rare occurrence but the fact that it happens at all suggests that some PAs are not taking the privilege of prescription writing as seriously as they should. Although some situations and practices fall in an ethical gray zone, this one is definitely black and should not be tolerated by physician or PA.

The Do's

1) Do review and countersign promptly those medical records written by your PA. Chart review is one of the primary methods physicians use to supervise their PAs. It's also an excellent opportunity to give your PA feedback, both positive and negative. The rule is that this review must take place within 24 hours of the PA/patient contact. To address a special problem posed by some practices, the BME let us know that they're understanding enough to recognize the difficulty met by physicians and PAs when a PA sees a patient in the office late Friday afternoon while the physician is making rounds in the hospital. If the team doesn't meet again until Monday morning, then the 24 hour limit is "understood" to mean by the next working day. A weekend stops the clock, in other words.

2) Do register your PA with the North Carolina Board of Pharmacy if you are going to have the PA *dispense* any medications (OTC medications can be dispensed by PAs without Board of Pharmacy permit). An occasional pharmaceutical sample may be dispensed by a PA provided it is entered on the medical record, is not a controlled substance or an excluded medication, and you countersign the record. Be aware of the definitions of "administering," "dispensing," and "prescribing" as defined by the North Carolina Board of Pharmacy.

3) Do insist that the PA who works for your practice wear a name tag which will prevent the PA from being misidentified as a physician. If life and the practice of medicine are considered a game in which the rules must be followed to play, then this next rule might sound a lot like the game of "trivial pursuit." The rule is that every PA must wear a name tag identifying himself as a "physician assistant," not just a "PA." Considering myself an empathetic observer of PA regulators, I can understand the strong feelings for this requirement. PAs perform traditional physician tasks and while most people know what "M.D." and "R.N." stand for, many people still don't know what "PA" means. The rule insures that patients and other involved parties do not confuse a PA with a physician. No PA should be permitted to avoid wearing his physician assistant name tag because of the flimsy excuse that name tags put holes in shirts, especially when clip-on name tags are available.

4) Do supervise your PA so that both you and your PA are comfortable and within safe and ethical medical practice standards in your community or hospital setting, and within the regulations of the BME and Board of Pharmacy.

5) Do encourage your PA to participate in local, state and national physician assistant organizations. Often, the annual cost of membership in such professional organizations can be offset by lower member rates at CME conferences and by having your PA sensitive to standards and changes in the PA profession.

More information about regulations or memberships can be easily obtained by writing to these addresses:

North Carolina Board of Medical Examiners
Suite 214, 222 North Person Street
Raleigh 27601
919/833-5321

North Carolina Academy of Physician Assistants
Box 27843
Raleigh 27611

North Carolina Board of Pharmacy
P.O. Box H
Carrboro 27510
919/942-4454

American Academy of Physician Assistants
Suite 300
1117 North 19th Street
Arlington, VA 22209
703/525-4200

6) Do encourage your PA to seek and maintain professional competency by participating in national certification examinations for PAs. The 24-month-long PA training program prepares a student in the basics of medicine, just as medical school provides the basics for postgraduate res-

idency training. The secret to success as a knowledgable and well-informed graduate PA lies in the ability to be a continual student and to build on the basics taught in the didactic and clinical training of the PA school. There is a difference between having 10 years' experience and having one year's experience 10 times over. If PAs are to grow as clinicians they must read, attend conferences, view videotapes, listen to colleagues; in short, they must learn every day. One method of testing basic knowledge is through the national certification examination, given after graduation and at six year intervals for recertification. PAs and those physicians who employ PAs should emphasize continuing medical education and national certification as a requirement for continued employment. We cannot afford to ask less of ourselves.

Resolving these problem areas will do much to make all of us better physician/PA teams. For those who feel it's all much too picky, perhaps a thought from Sir William Osler will convince you.

"Things cannot always go your way. Learn to accept in silence the minor aggravations, cultivate the gift of taciturnity and consume your own smoke with an extra draught of hard work, so that those about you may not be annoyed with the dust and soot of your complaints."

EDITORIAL

Thoughts on the PA/Physician Team

F. Maxton Mauney, Jr., M.D.

THE practical and timely paper by James E. Hill, Jr., P.A.-C, M.Ed., concerning the "Do's and Don'ts of Responsible PA Practice," is worth taking a minute to review whether you use physician "extenders" or not. For those who do use either nurse practitioners or PAs it serves to point out the most common pitfalls in this important arena of health care delivery and, in a practical, common sense manner, suggests some useful tips about strengthening and building upon what has for the most part proved to be a beneficial and effective relationship. There are currently more than 500 PAs registered under the physicians' license in North Carolina, and an additional 406 nurse practitioners are also working with physicians in our state. Approximately one out of every ten physicians licensed in the state has either direct or secondary supervision of a physician assistant.

At the time the editor of this *Journal* embarked on the formal training of assistants to the physician, I doubt that anyone would have predicted the success that this program has had, not only in North Carolina but across the country. While many are greatly concerned about the upcoming physician "glut," there are no similar concerns about class size in the 50 or so PA training programs nationwide. Several PA schools have closed in the past couple of years as manpower training grants have phased out and as the perceived needs for these talented men and women have decreased. At the same time, as Chairman of the Joint Review Committee for Physician Assistants, which reviews and accredits all PA training programs nationwide, I know that three or four prominent schools across the nation are considering establishing *new* PA training programs. The success that "primary care providers" and specialists in almost every field have realized with the utilization of PAs has been enormous and far-reaching, touching all levels of the health care delivery system.

Unfortunately, as is inevitable, there have been abuses and misuse of the physician extender concept not only by the PAs and nurse practitioners themselves, but also by physicians who either misunderstand the role of the supervising physician or improperly use the "extender."

Those who have not been directly involved in this teamplay hear only the loud voices of critics of the system, who are usually quite vocal. I have been privileged to participate in the development and use of the PA concept as a faculty member at Duke in the Department of Surgery in the late 1960s, as a physician and supervising employer in Asheville of a number of physician assistants since 1970, and as a representative of the American College of Surgeons on the Accreditation Review Committee for Training Programs nationwide for PAs since 1980. I have also had the opportunity of chairing the North Carolina Medical Society Committee on Allied Health, meeting with this Committee as a commissioner, and working with the North Carolina Academy of Physician Assistants as a physician advisor for several years. The commitment of the majority of PAs to maintaining excellent standards, fostering continuing medical education, and solving problems in the practice arena has been exemplary. Very few groups of allied health professionals strive any harder to develop close, collaborative and dependent relationships with physicians than the PAs in this state. We as physician employers and supervising doctors need to be pro-active and understanding in learning how to use PAs appropriately without putting them out on a limb with the bad habits listed under the "don'ts" in this timely paper.

Jim Hill and his colleagues are to be commended for their honesty and openness in communicating the issues to all physicians.

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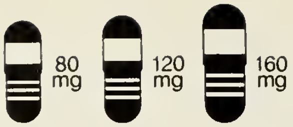

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure, intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

REFERENCES

1. Holland OB, Nixon JV, Kuhnert L: Diuretic-induced ventricular ectopic activity. *Am J Med* 1981;70:762-768. **2.** Holme I, Helgeland A, Hjermann I, et al: Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. *JAMA* 1984;251:1298-1299.

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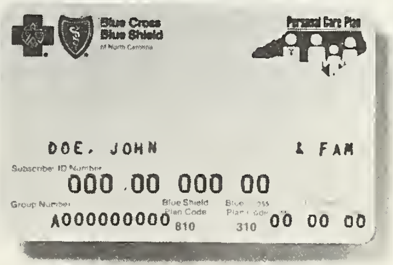

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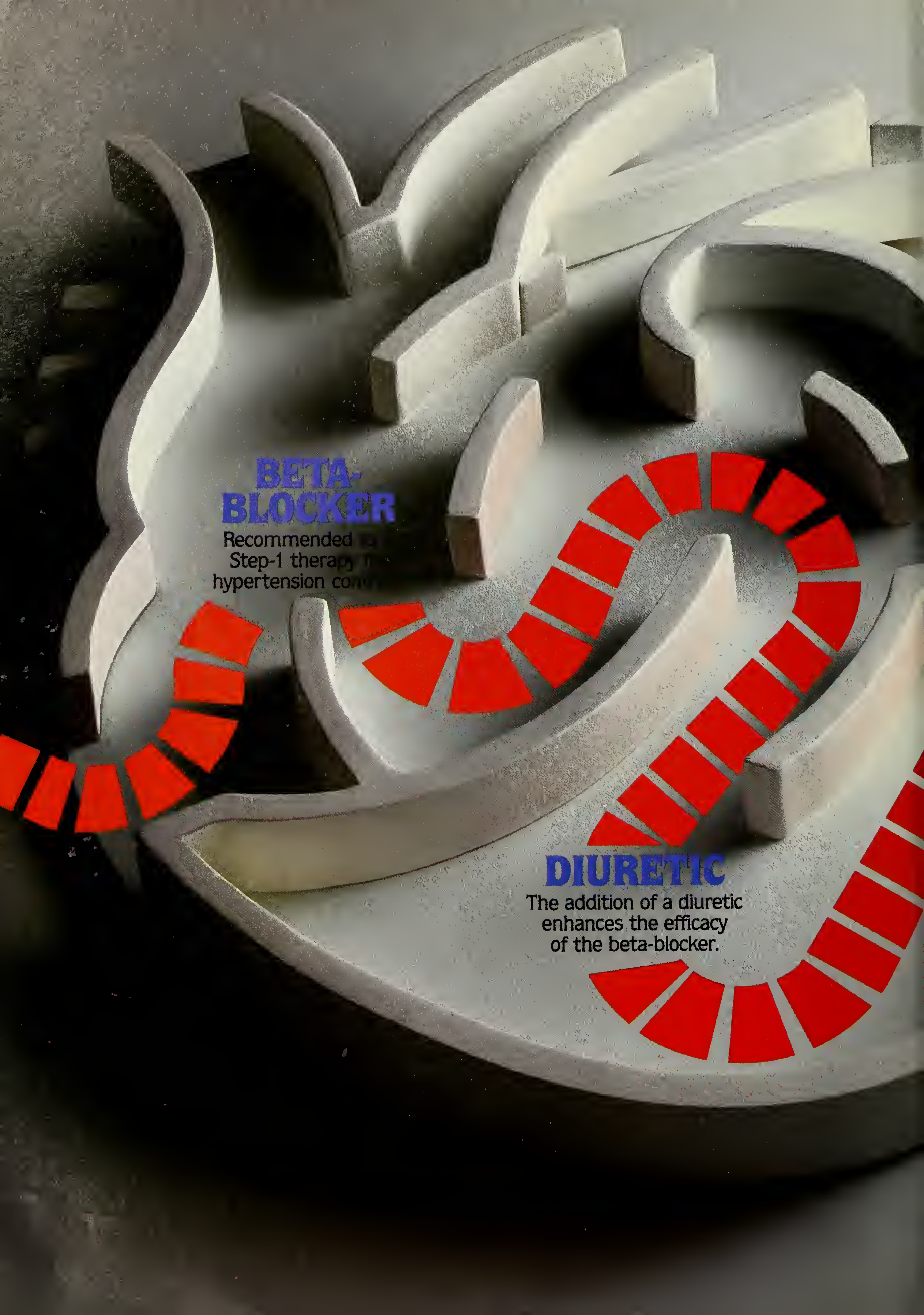

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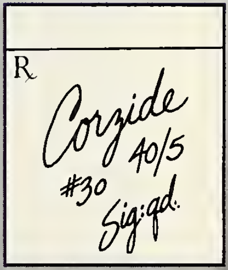

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*Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. The 1984 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 144:1045-1057, 1984.

Please see brief summary of prescribing information on following page

CORZIDE®

(nadolol-bendroflumethiazide tablets)

CORZIDE® 40/5
CORZIDE® 80/5
Nadolol-Bendroflumethiazide Tablets

DESCRIPTION: CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration combines two antihypertensive agents: CORGARD® (nadolol), a nonselective beta-adrenergic blocking agent, and NATURETIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations: 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide.

CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). **Bendroflumethiazide** — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS: Nadolol — **Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually, if possible).

> **Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal** — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — **Nadolol** — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and G.I. disturbances such as nausea and vomiting Observe patients for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, *Bendroflumethiazide*, and PRECAUTIONS, *General*, *Bendroflumethiazide)*.

Drug Interactions — **Nadolol** — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents: **Anesthetics, general** — exaggeration of anesthetic-induced hypotension (see WARNINGS, *Nadolol*, *Major Surgery)*. **Antidiabetic drugs (oral agents and insulin)** — hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, *Nadolol*, *Diabetes* and *Hypoglycemia)*. **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect; monitor closely for evidence of hypotension and/or excessive bradycardia

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics: **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabatic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of antidiabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or peripheral adrenergic blocking drugs** — potentiated effect. **Preanesthetic and anesthetic agents** — effects may be potentiated, adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, *General*, *Bendroflumethiazide)*.

Carcinogenesis, Mutagenesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed

Pregnancy — **Teratogenic Effects** — **Nadolol** — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose, no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potentia benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Anima reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus; these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cardiovascular** — Bradycardia with heart rates o less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms o peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported, intensification of AV block is a known effect of beta blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdomina discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling, weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol. The following adverse reactions may also occur: **Central Nervous System** — reversible mental depression progressing to catatonia, visual disturbances hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss; emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis ischemic colitis. **Hematologic** — agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat, laryngospasm respiratory distress **Miscellaneous** — reversible alopecia; Peyronie's disease erythematous rash; arterial insufficiency

Bendroflumethiazide — **Gastrointestinal System** — anorexia, gastric irritation, nausea vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia **Dermatologic-Hypersensitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestina irritation and hypermotility may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, employ the following measures, as appropriate. **Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg) If there is no response to vaga blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation **Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a beta$_2$ stimulating agent and/or a theophylline derivative. **Stupor or Coma** — Supportive therapy as warranted. **Gastrointestinal Effects** — Symptomatic treatment as needed. **BUN and/o Serum Electrolyte Abnormalities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100

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Bulletin Board

Continuing Medical Education

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IN STATE

November 14-15
Clinical Teaching and Evaluation of Clinical Performance
Place: Chapel Hill
Credit: 12 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

November 20
Endocrinology for the Lifetime of the Female
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

December 5-7
Fourth Comprehensive Symposium on Breast Disease
Place: Winston-Salem
Credit: 16 hours Category I AMA
Fee: $350.00
Info: Center for Medical Ultrasound, Bowman Gray, Winston-Salem 27103. 919/748-4505

December 5-7
Microcomputers in Medical Education
Place: Chapel Hill
Credit: 18 hours Category I AMA, NCMS
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

December 7
UNC Ophthalmology Resident's Day
Place: Chapel Hill
Info: Baird S. Grimson, M.D., 617 Clinical Sciences Building 229H, UNC, Chapel Hill 27514. 919/966-5296

December 12
Controversies in Transplantation
Place: Chapel Hill
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

December 18
New Uses of Calcium Channel Blockers
Place: Sanford
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage Street, Sanford 27330. 919/774-6518

January 10-11, 1986
Advanced Cardiac Life Support
Place: Chapel Hill
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

January 30, 1986
Controversies in Transplantation
Place: Chapel Hill
Credit: 7 hours Category 1 AMA
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

OUT OF STATE

December 5
A Seminar on Legal Medicine
Place: Johnson City, TN
Credit: 7.25 hours Category I AMA, 7 hours AAFP
Fee: $75
Info: Sue Hutchinson, Box 19660A, Quillen-Dishner College of Medicine, Johnson City, TN 37614. 615/928-6426, ext. 204

January 24-26
Winter Conference on Geriatrics
Place: Hot Springs, VA
Info: Mary Anna Hendley, NC Academy of Family Physicians, Box 20146, Raleigh 27619. 919/781-6467

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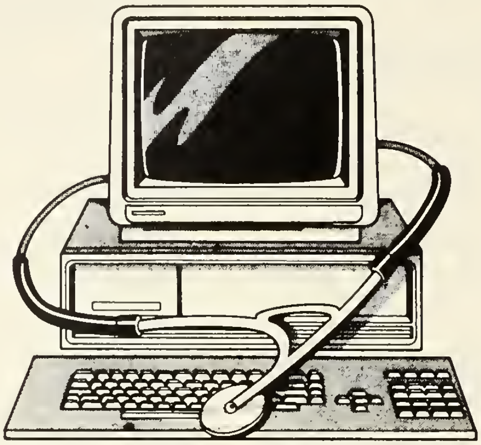

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Letters to the Editor

What To Do About Tobacco?

To the Editor:

I congratulate Dr. Moffett and Dr. Stead on their excellent Letter and Comment regarding tobacco in the September issue of the NCMJ (46:493). Physicians finally have stopped allowing the pretense that the link between cigarette smoking and disease is doubtful. The proof of the association is overwhelming.

Dr. Moffett's suggestions to the tobacco companies would be wonderful — if the changes were likely. But as lawyers remark: "Tobacco companies are not eleemosynary institutions." Industries seldom act in the public interest when such actions oppose their own economic interests.

There is a simple way to decrease our dependence on tobacco. Provide such high price supports for cotton, corn, vegetables, fruits, and other valuable crops that any efficient farmer can make a good living by planting them. Discontinue allotments and price supports for tobacco. Prohibit public billboard advertisements for tobacco. Increase the tax on tobacco products yearly until consumption falls significantly, but do not make the tax so high that people begin to bootleg tobacco.

An extra advantage of this course of action would be to lessen the glaring governmental inconsistency which makes marijuana illegal and growing it a crime, while tobacco receives price supports and beer advertisements rule the TV screens. We cannot teach our youth to respect prohibitions that seem arbitrary and illogical compared with the incentives and freedoms given rather similar products.

Of course, my suggestions have little chance of being accepted in the next few years. In an overpopulated society, such as the USA, many people have few alternative ways of making a living. The leaders and people in favorable positions become afraid of proposed changes which might jeopardize their economic security. In North Carolina today, a politician who ran on the above platform regarding tobacco would be lucky to receive 5% of the votes. Nevertheless, the preceding suggestions (or something similar) eventually are almost sure to be adopted. Tobacco, once a mighty King, will become a weed in the farmer's garden.

Albert D. Warshauer, M.D.
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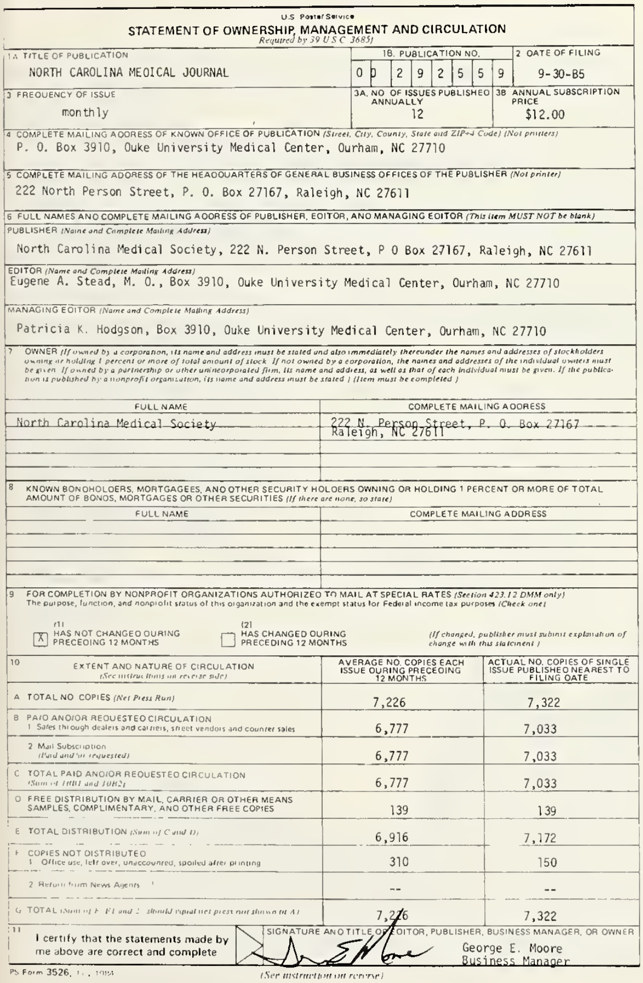

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More on Coccydynia

To the Editor:

Another cause of coccydynia was recently reported by E. A. Mortimer, M.D.: two teenage girls developed coccyx pain when slouching in hard classroom seats while wearing tight blue jeans (Pediatrics 1985;76:138). One of the patients was concerned enough to seek orthopedic evaluation, but Dr. Mortimer recognized that the stiff reinforced jean seams caused coccyx trauma.

Based on this experience, Dr. Mortimer has an interesting comment about our Case 3, the young man on the motorcycle who suffered from tailbone pain (NCMJ 1985;46:209-12):

"I notice that the guy sitting on the motorcycle and holding a beer (Case 3) is wearing blue jeans: in his instance the etiology may be multi-factorial. It would then have to be called the Harley-Davidson-Jordache Syndrome."

Linda Frazier, M.D.
Division of General Internal Medicine
Duke University Medical Center
Durham 27710

Duke's Family Medicine

To the Editor:

I read with interest Dr. Robert Sullivan's review of the Family Medicine program at Duke (NCMJ 1985;46:329-31), Dr. Harvey Estes, Jr.'s Family Medicine at Duke: A follow up (NCMJ 1985;46:443-4) and George T. Wolff's and William A. Hensel's letters to the editor about the same subject (NCMJ 1985;46:493-5). They outlined many powerful currents that have affected this watershed event. I should like to suggest another angle that I think is both supplementary and complementary of the ideas presented by these writers.

Much of the struggle that Family Medicine departments and Family Medicine practitioners face in the internecine warfare of the tertiary medical center revolves around our own failure to earn our academic spurs. We can easily demonstrate the family physician's superiority at delivering medical care, and this delivery includes the efficient and effective utilization of the skills and talents of our subspecialist colleagues. We may successfully rest our future existence on this strength, and as this strength develops, it will enhance our relationship with our subspecialist colleagues. But, we will not successfully stand toe to toe with them in academe until we do research on disease processes that is better then theirs.

Intellectual strength belongs to those who break new ground.

And we have several characteristics of family practice that present us with the opportunity to do exactly that.

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Secondly, such diseases as the sexually transmitted diseases should be almost the exclusive province of the family physician. The internist and infectious disease specialist has to move out of his usual age group to deal with these diseases. Syphilis is obviously no longer the province of the dermatologist. The urologist may know a bit about prostatitis, but is often unfamiliar with the cervix. The gynecologist knows a great deal about the cervix, but almost nothing about the prostate. The pediatrician begins to blush when his patients reach this age.

And most importantly, family physicians should be least guilty of all physicians of thinking in "pigeon holes." We should understand the interrelationships between the psycho pharmacology of depression and the pharmaco therapeutics of hypertension, for example. The internist is so busy treating the high blood pressure that he has little interest in depression, and the psychiatrist is so busy with the depression that he has little interest in hypertension. We see both!

Family physicians should be prepared to undertake these explorations and to break new ground.

John R. Dykers, Jr., M.D.
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Frank L. Engel, M.D. (1913-1962), whose photo is reproduced below, wrote the original grant application to establish a general clinical research center at Duke University Medical Center. This month marks the end of the 25th year in the life of the Rankin Clinical Research Unit . . . page 645

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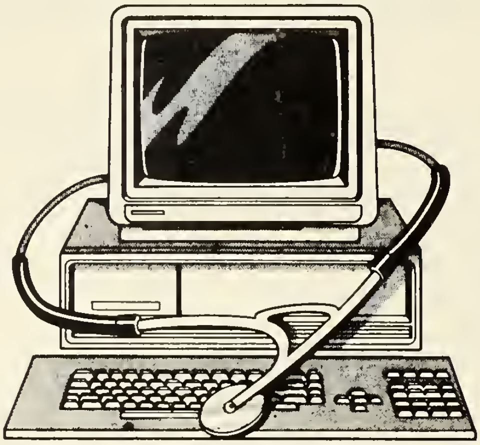

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On Dating, Marriage and Other Strange Relationships: The Future of Singular Hospitals

Harry A. Nurkin, Ph.D.

- *The dating game turns serious when the parties are hospitals and the product is health care.*

IN the world of business, corporate marriages are a familiar phenomenon. Often industrial mergers occur for purposes of diversification of product line, improved market penetration, economies of scale, strength and/or survival. While some industrial mergers are characterized as "unfriendly takeovers," for the most part the joining of two businesses or the merger of smaller businesses into larger corporate structures is considered to be routine and often healthy. One also sees marriages occur in other stable institutions and enterprises in our society. For example, institutions of higher learning join together for economic reasons as well as for more effective provision of the process of learning and the development of new knowledge. Churches and religious orders marry for the purpose of creating stronger congregations in order to carry out more effectively the mission of the particular denomination or church. Human beings marry for a variety of purposes, but such unions are generally based on a mutual desire to live, to work and to love together so that the parties of the union benefit far greater than they would have as separate individuals.

But when hospitals consider marrying, or other types of symbiotic relationships, unusual emotions erupt. Perhaps such mergers, marriages and other strange relationships involving hospitals engender emotion and lengthy discussion because such activity is a relatively new phenomenon in the hospital business.

Hospitals have been created for social and scientific purposes in over 7,000 locations in the United States. Hospitals are the most unique of modern enterprises according to management theorist Peter Drucker. They provide services that most recipients would prefer not to need. With the exception of normal births, most activities carried on in hospitals place the recipients of care in an atypical and unnatural environment where their bodies, internal chemistries, organs, and personality are examined, probed, punctured, and excised, in an attempt to resolve and/or cure afflictions that cause great anxiety and fear. In addition, hospitals are unique enterprises because of the myriad of formal and informal relationships brought to bear at the point of service. Physicians, with the exception of teaching physicians and hospital-based specialists, are private entrepreneurs who practice voluntarily at hospitals. In this capacity, physicians interface with a potpourri of workers in health professional and support capacities to carry out the directions of the physician in order to diagnose, examine and provide therapeutic modalities for the care and treatment of patients.

Hospitals are also the prime example of a service industry. Generally the products of hospital activity are human-to-human services as compared with manufacturing or sales of products in the typical industrial setting. Most patients leave the hospital experience without tangible evidence of the experience, other than a general feeling of well being and elimination of anxiety and fear related to disease and injury. Unlike institutions of higher education, diplomas are not awarded. Unlike sales companies, no product can be viewed, used or worn by the purchaser of the hospital service.

Although hospitals are unique enterprises, communities regard them not only as necessities, but also as symbols of pride. Yet there exists in the midst of the pride in community hospitals an identifiable love-hate relationship. Generally, community citizens are prideful about the resources and technology and buildings called hospitals, yet the emotions of fear and anxiety and the potential for death also are apparent in the identification with hospitals.

In recent years, hospitals have also become the subject of much discussion related to the cost of care. Headlines proclaim that health care cost, of which a sizable proportion relates to hospital cost, has risen at an inflationary rate in excess of 18% annually, to the extent that almost 12% of the gross national product of our country can be related to expenditures for keeping our populous healthy. Of course such dramatic increases in the cost of health care create additional anxiety on the part of citizens in communities throughout our country, as well as business leaders who buy insurance for employees, tax payers who sponsor health care through taxation, insurance companies who provide various types of health care insurance, and others who are generally concerned about the rapid increase in health care cost.

In addition to such broad and varied emotional responses to hospitals as necessary but troubling enterprises, a broader social view of hospitals and health care in our country has been difficult to define. Because of the increasing cost to provide care through hospitals, we have wrestled with how

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From The Charlotte-Mecklenburg Hospital Authority, Box 32861, Charlotte 28232.

this societal need should be balanced against other needs in light of available financial resources. Generally, Americans accept a social philosophy that supports the "highest possible quality" and "unlimited access" but also believe that such quality and access be provided at reasonable costs.

In a strained economy individual emotional responses to hospitals and the health care provided therein cause us to examine our collective social and philosophical conscience regarding whether the traditional system of hospitals should continue or whether new corporate formats should be created to provide necessary services at the highest possible quality with unlimited access, but at a controlled cost. These are difficult and often unanswerable dilemmas that we face.

Those who serve as members of Boards of Trustees of hospitals and managers of such facilities currently face a troubled environment. Uniformly, such persons are buffeted with complaints about the high cost of care provided by hospitals. Simultaneously, communities desire to have the most modern, up-to-date technology and facilities and the most skilled health professional and support personnel available. No citizen wants to believe that when he needs hospital care there will be inadequate physical facilities, outdated diagnostic and therapeutic equipment or too few health professional and support personnel. As the science and art of medicine progress, physicians desire to have the most modern and effective diagnostic and therapeutic tools available to assist in the care of the physician's patient in the laboratory or clinical environment known as a hospital. Physicians are also being buffeted by complaints and concerns on the part of business and industry and individual patients regarding the high cost of health care and the apparent inability of the health care system to work efficiently and effectively.

Our desire for super-specialization has developed to the extent that not every hospital is capable of dealing with all diseases and injuries. In earlier times hospitals provided all types of care and all types of equipment necessary for the physician to practice his trade. Today, in many communities a broad range of specialty facilities exists in addition to general facilities that can care for all maladies. Patients and physicians are forced to make decisions regarding the appropriate hospital to use depending on the disease or injury afflicting the patient. The relationships among the hospitals, patients, physicians, trustees, providers, insurers, administrators and other health professionals are indeed strained because of these compelling pressures of societal need, quality, access, competition and cost.

The most pressing issue facing the family of health care relationships today is the issue of cost. If, indeed, appropriate health care is a basic human right in America, how much can we afford to spend on this right as opposed to other human necessities and societal needs?

One of the ways to address the dilemma we all face is to determine whether more efficient, alternative delivery systems can replace what we have known to be the hospital system in our country. Alternative delivery systems can take the forms of mergers, partnerships and other intimate relationships among and between hospitals. In the decade of the 90s, we will see a change in the corporate structure of hospitals throughout the State of North Carolina as well as other states in our country. Because most hospitals have operated as singular corporate entities, little in the way of economies of scale to contain costs has been available. In essence, hospitals have been as self centered and jealous of their singular enterprises as have been communities.

Until the burden of regulated payment systems and the advent of for-profit multiple hospital systems emerged in the decade of the 70s, singular hospital units believed they could survive financially and provide all elements needed by physicians and patients on a continuing basis. The decade of the 90s will witness a proliferation of new corporate designs as hospitals discover that "going it alone" does not work, and they begin to maneuver for secure positions in a highly competitive marketplace filled with increased risks and continuing complaints about efficiency, effectiveness, and the high cost of care.

Multiple hospital systems are already growing rapidly. Centrally managed chains of health delivery facilities now provide services to patients in over 12,000 facilities. This number combines hospitals, ambulatory centers, nursing homes, rest homes and other institutional sites for health care. It has been predicted that by 1990 investor-owned hospital chains will constitute 19% of our nation's hospitals and 23% by 1995, up from 14% in 1982. Singular, not-for-profit hospitals, once 100% of the market, will fall to less than 50% by 1995. It is estimated that over 40% of non-governmental hospitals will be owned, leased or controlled by multi-hospital systems by 1995, an increase of one-third over 1982. Much of the growth in multi-hospital systems will be generated by investor-owned or for-profit hospital chains, but not-for-profit systems will merge, marry or live together strictly for survival purposes by the decade of the 90s.

Mergers, marriages and other strange relationships will be based on the need of singular hospital units to protect or expand their market areas to achieve economies of scale by spreading the high cost of personnel and technology in order to survive in the next decade.

The reasons are easy to understand. In addition to economies of scale, singular hospitals that merge into larger corporate entities will also have greater access to capital, increased reimbursement from cost-based payors, reduced regulatory constraints, and to a lesser degree limited liability for certain operations within the hospital organization. In addition, hospitals in multi-hospital systems will begin to enter non-traditional business ventures as a way to offset the high cost of health care and limited reimbursement from regulated governmental agencies and commercial insurance companies.

Similar to human bonding through marriage, such mergers, marriages and other affiliations will not occur without trauma. For centuries hospitals have been singularly owned and operated, and the community pride and spirit of those singular units will be forced to give way to the good of a greater need and to provide high quality and access at reasonable costs. There are examples in the State of North Carolina of multi-hospital system marriages. In Charlotte, the Charlotte-Mecklenburg Hospital Authority was created by an act of the legislature in 1943 to allow for economies of scale, elimination of duplication and protection against some of the forces that now impinge against hospitals. This forward-thinking legislation, created 42 years ago, now supports a system that includes a large teaching hospital of 777 beds, a rehabilitation hospital of 88 beds, a primary and secondary hospital of 130 beds, a skilled and intermediate nursing home facility of 282 beds, a rest home of 205 beds, several primary care facilities, emergency and ambulatory care facilities and an institute for health promotion. In Raleigh the Wake County Hospital System is made up of five institutions bonded together by economic, social and clinical needs. Sun Health, a multi-hospital ownership and management firm based in Charlotte, owns or manages nearly 50 institutions throughout the southeastern United States. This company also provides shared services for a number of other institutions in North Carolina and South Carolina through contractual relationships. In addition to these examples there are nursing home chains, rest home chains and investor-owned for-profit hospital systems operating multiple units in our State.

What does this portend for the future? For smaller hospitals in rural or suburban areas, the current economic facts of life are not promising for long-term survival. Access to capital, patient referral patterns, and the recruitment of primary and specialty physicians continue to be problems for smaller communities in the State of North Carolina. Without these essentials, smaller hospitals in smaller communities in our state will find it increasingly difficult to stay abreast of technology and provide to physicians and their patients the type of technology and care required to deal with current diseases and injuries at reasonable cost.

The dating game has already begun. Many larger hospitals in urban areas are courting smaller institutions, offering large sums of money to purchase or manage their facilities. Health Maintenance Organizations (HMOs) have entered North Carolina because market surveys show that our state is fertile for the introduction of this additional way of providing physician and hospital care at lower costs. In other states HMOs own their own hospitals and ambulatory facilities.

Obviously the marriages, mergers, dating relationships and other informal interactions are attractive to those who pay for care. Employers and insurance companies encourage the amalgamation of entities such as hospitals in order to reduce duplication and, therefore, the cost of health care.

The problems are also obvious. No singular hospital with the pride of history and performance wishes to give up its identity to a larger group or to be taken over or otherwise usurped by a larger corporation. Physicians have reasonable and understandable anxieties regarding such activities because there is no guarantee that the essential elements of pride and quality will be maintained as hospital mergers, marriages and other relationships continue in the State of North Carolina.

Nationally, the examples of merged hospital facilities are many and successful. In the State of North Carolina there are examples in Charlotte, Raleigh and other cities where facilities have merged into larger groupings for the benefit of the population, the practicing physician and cost. The forms of such relationships are many and varied. The growth has been so rapid that discussions now center around antitrust implications of controlling the market place.

Physicians are also concerned that larger corporations will be less willing to offer an ear to the physician or to invite the physician into the corporate board room for major policy decision making.

In our rapidly changing environment, each hospital must evaluate its strengths and weaknesses, its economic environment now and in the future in order to decide the most appropriate avenue of independence or merger for security. Competition has spurred the desire to reach new markets but also to share risks while obtaining capital and diversified revenue sources through mergers and other acquisitional corporate structures.

As admissions to hospitals have declined over the past five years the ability of singular hospital units to survive has diminished. As ambulatory services continue to take a larger chunk of the traditional hospital service market, singular hospital units will face additional survival questions.

As with industrial mergers and other types of organizational marriages, the basic questions will be: Can physicians and their patients be better served by the traditional singular hospital unit or can economies of scale and access to capital and new technology improve patient care through merging or joining multiple hospital systems? Will the benefit be to physicians, patients and those who pay the cost of health care?

There are no ready answers to the questions. One must approach marriage or merger with caution so as not to damage irreparably the good and important elements of our health care system.

Hospitals besieged by new competitors and pressured to cut costs are entering a new and unfamiliar environment. As admissions decline and the government's new prospective payment system is making itself felt, hospitals throughout our state are feeling the pinch. Nonprofit hospitals face competition from newer for-profit providers of health care. There are advantages and disadvantages for hospitals to consider, such as downsizing, diversification, joint ventures, as well as mergers and other types of corporate affiliations. Those singular hospitals that do not wish to merge with larger systems may attempt a joint venture with other singular hospitals in an effort to find the benefits of marriage without actually consummating the marriage. Merger with other hospitals or larger corporations is often seen as the last resort for singular hospitals. Yet in many cases it may be the best strategy. Hospitals that need large amounts of capital, recruitment of physicians, the purchase of technology and the maintenance or replacement of older buildings may find that merger with larger hospitals or multi-hospital systems is the only answer to survival.

The failure or closure of some smaller hospitals in the State of North Carolina is probably inevitable. This year at least three facilities have either closed or come near to failure financially. It is not in the public interest to continue to have singular hospitals operating in weakened financial conditions fighting to survive in our communities. The strategies for survival are available, and many singular institutions will respond to threats to their survival by marrying, merging or establishing relationships with other hospitals.

A Duke Administrator Surveys the Current Scene

Duncan Yaggy, Ph.D

DR. Nurkin has put his finger on a problem that worries many communities in North Carolina, for the survival of rural, independent hospitals is threatened on four sides at once:

- Pressures to limit the growth in expenditures for health care are reducing hospitalization. Hospital utilization has dropped sharply the last three years, and it will continue dropping for several years more.
- Public and physician perception that large urban hospitals can provide more comprehensive services is taking patients out of rural hospitals. Rapid development in the Piedmont, along the coast, and in other parts of the state will bring more residents of rural areas to the cities and accelerate the trend.
- It is hard to raise the capital required to renovate hospitals and keep them up to date. Many of our rural hospitals were built during the 1940s and 1950s and require reconstruction or extensive renovation simply to operate efficiently. Declining occupancies make it seem essential that they renovate, but they will also make it more difficult to find the funds.
- The growth of health maintenance organizations, preferred provider organizations, and other prepaid plan arrangements will bring into the health care market buyers who will use the competition between hospitals with empty beds to compel substantial discounts.

Whether to hold on to their patients, protect their revenues, gain access to the capital they require, or share in the economies of scale that come with participation in a larger system, independent hospitals are entering all manner of new relationships. Some are joining multi-hospital systems, while others are joining with their physicians to create prepaid plans, and still others are creating ties with ambulatory care providers, nursing homes, and home health agencies to create health care service organizations providing a full range of services.

As Dr. Nurkin points out, the difficulty of developing networking arrangements is formidable, and hospital boards accustomed to concern with acute inpatient services and to independence may find the transition awkward and difficult. But for many hospitals, large and especially small, there is no choice.

From Duke University Medical Center, Durham 27710.

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

PROFESSIONAL USE INFORMATION

cardizem®
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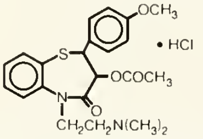
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence. tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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Do Not Resuscitate Orders in Nursing Homes: The Need for Physicians to Communicate and to Document

Paul Beck, M.D.

- *Physicians who care for patients in nursing homes should read this article on DNRs, which was written by the Chairman of NCMS' Committee on Aging.*

DURING the past year, the Committee on Aging of the North Carolina Medical Society was asked to consider problems encountered regarding the interpretation of the North Carolina Right to Natural Death Act as it applied to Do Not Resuscitate (DNR) orders in North Carolina nursing homes. As physicians have already learned in the hospital setting, there are differences of opinion about the interpretation of this act by nursing home physicians, administrators, and agencies that review the nursing homes. This issue is complex and its application in the nursing home setting is further complicated by the frequent lack of documentation in the nursing home patient records about "do not resuscitate" requests that have been made by patients and their families. In nursing homes in particular, physicians often fail to document their discussions with families about their desired goals and outcomes for the patient.

Physicians may make notable contributions to the well-being of nursing home patients, their families, and their caregivers (the nursing home staff) by considerate development of the patient care plan at the time of admission to the nursing home. However, appropriate solutions to the "do not resuscitate" problem require careful consideration by physicians of ethical issues regarding palliative and supportive care. These include 1) ways to ascertain the wishes of the patient and family with regard to treatment goals and outcomes, including their wishes about life support measures in the event of a life-threatening event; 2) legal mechanisms for documenting the patient's wishes and care plans; 3) ways to incorporate these wishes into a **comprehensive** care plan for the patient before, during and between nursing home admissions. Finally, none of these considerations will bear fruit unless the physician continues to be involved in the care of the patient. This will be facilitated when patients and physicians develop mechanisms for insuring that physicians are adequately reimbursed for the time and services that they render to their nursing home patients.

Ways to Ascertain the Patient's Wishes

The salient feature of top-quality decision making in health care is collaboration between a qualified physician and a competent patient.[1] The physician makes every attempt to insure that the patient knows about the treatment options that might be advantageous (including no treatment); the patient informs the physician about his or her own values or preferences. This process of shared communication and experiences will usually lead to an agreement about the best course to pursue. When agreement does not occur, then cultural and legal values in our society require that the patient bear both the responsibility and the authority for his or her own choice.

Obviously, some potential options are not available to either the physician or the patient. For example, the physician cannot legally or ethically be asked to administer a poison or a toxic drug to a patient or give transfusions to a patient who will not accept them. Similarly, patients may not be able to accept certain options because of inadequate finances, or transportation, or the unavailability of necessary resources in the area where the patient lives. Options should not be excluded, however, because of an unilateral assessment of the patient's wishes or quality of life.

It is essential that the physician strive to enhance the ability of the patient to make good decisions. Coercion and manipulation must be avoided by such maneuvers as unfair, biased presentation of the facts, trauma, threats of abondonment, or restrictions of the patient's ability to handle activities of daily living. Similarly, it is important that the patient receives essential emotional support, effective counseling, and adequate time to assess and to evaluate all relevant information. Physicians should attempt to encourage clarification of values and priorities and to minimize mind altering drugs or procedures. The patient's confidence and self-respect should be stimulated by having the patient make many minor decisions, mobilizing the support of significant family and friends, and clarifying the nature of the choices by encouraging the patient to meet others who have made similar choices. When patients are not able to make reasonable choices that reflect their own values (because of excessive weakness, depression, or altered

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state of consciousness), the attending physician must be responsible for recognizing this deficit and for implementing appropriate corrective steps. The ethical mandate is clear that the physician should assess the patient's capacity to enter into decision making and should assure that good choices are made on behalf of each patient who has inadequate judgment capabilities.

There are several alternate ways in which the patient may indicate to the physician his/her capacity for participating in decisions about medical care. First, the patient may be able to demonstrate an appreciation of the seriousness of the choice that he/she is making. A reasonable standard for the patient's decision is the same as a ''prudent person in similar circumstances.'' This lay person standard is not the same as the ''prevailing standard'' of medical practice. Similarly, psychiatric assessment for substantial deficits in cognitive emotional functioning may be helpful, but not determinative, because even people with major psychoses may be able to make some decisions that are unaffected by their psychoses. Second, the patient may name his/her preferred surrogate and give that person instructions through a ''durable power of attorney'' (to be defined in the next section). When the patient is not able to make serious decisions about his/her own choices, the attending physician should identify a surrogate who can collaborate in the decision making on behalf of the patient. Finally, the patient may wish to turn over significant treatment choices to his/her physician. As long as the patient realizes the implications of these decisions and realizes that he/she could have made them, and as long as the physician is willing to accept this role, delegation of the final decisions to the physician is quite acceptable and should be documented.

As in all medical care, physicians are well advised to document carefully the content of the discussions with their patients and the processes utilized in making these decisions. Both ideally and practically, these decisions should be made before the patient is admitted to the nursing home.

Ways to Determine the Wishes of the Family

The prognosis of patients admitted to nursing homes is usually well known to their family caregivers long before the frail patient is admitted to a nursing home. Consequently, these family members often develop opinions about the relative merits of supportive versus curative care. As shown by Smallegan[2] and by Knight and Walker,[3] the decision to admit a relative to a nursing home is generally made only after long deliberation and consideration by family members. Most of the patients admitted to nursing homes have required a great deal of help (usually by spouses, daughters and/or sons) long before the patients were admitted to the nursing home. In at least two-thirds of the ill elderly patients, the breaking point generally occurred when the level of care needed was high, particularly when supervision or care was needed 24 hours a day.

The major problems precipitating admission to nursing homes were confusion and an inability to walk well. At least 60% of the patients needed some assistance in five or more of the standard activities of daily living, particularly bathing. Eighty-eight percent of the patients had recognized the existence of problems for more than a year; more than half of them or their families had been worried about these problems for a year or longer. Families and nursing home staff reported an average of just over four health problems for each person, with at least one of these problems having become more acute during the month preceding admission. Health problems that most often precipitated admission to skilled nursing facilities included fractures, strokes, cancer, pulmonary disease and pain. For intermediate care facilities the major precipitating problems were difficult behavior (25% of those admitted), confusion, incontinence, debility, and unwillingness to eat. Falls were also a frequent precipitating complaint. From the family's standpoint, about a third of the admissions occurred when the family felt that the new problems of caring for the patient required too much work. Exhaustion or death of the caregiver accounted for about 20% of the admissions.

Physicians are also aware of the decline of these patients before their admissions to nursing homes. As shown by Lewis, Cretin, and Kane,[4] 54% of the patients admitted to a variety of California nursing homes over a two-year period were transferred frequently between hospitals and nursing homes. Physicians were obviously responsible for the patients during their care in hospital. In addition, the current prospective reimbursement mechanism for hospitalized Medicare and Medicaid patients (Diagnosis Related Groups — DRGs) fosters the tendency to send patients to nursing homes in order to promote early discharge from the hospital. Paradoxically, the DRG mechanism is likely to exacerbate the tendency to shuttle nursing home patients back to hospitals for relatively minor problems, provided that the interval between hospitalizations is sufficiently long. In any case, the physician is usually able to inquire of both the patient and family about their wishes for life support measures not only in the hospital, but also at the time that they plan for transfer to the nursing home.

Legal Mechanisms for Documenting the Patient's Wishes: Advance Directives

Making life or death decisions becomes measurably easier when the patient expresses his values and wishes. Both the patient's family and the physician or other health care givers feel much more comfortable making such a decision when the patient's wishes are known. In our culture, legal requirements mandate that the patient be presumed competent and able to make informed decisions. In these matters, competency or decision-making capacity can be defined in terms of an individual's capability to understand information relevant to the medical decision at hand and to reason about relevant alternatives against the background of stable personal values and life goals.

These decisions can be made before the fact as well as at the time of a critical event. An ''advance directive'' is an oral or written instruction prepared by an individual concerning his/her health care in the event of later loss of competence or decision-making capacity.[5] All of these mechanisms require legal consultation and need to be filed and/or approved by a court. The North Carolina Right to Natural Death Act[6] provides for patients to make legal documents, i.e., ''living wills,'' in which the nature and type of life-supporting mechanisms to be limited or used can be specifically stated. This Right to Natural Death Act is, by its own language, not limited to Living Wills. Thus, other written mechanisms can be considered. For the patient who wishes to insure that all resuscitative options be considered, it is possible to write a "Directive to Provide Maximum Care" statement which specifically requests the physician to undertake all reasonable mechanisms for providing life support in the event of cardio-respiratory failure.[7]

Another mechanism, "durable power of attorney," is embodied in Chapter 32A of the North Carolina General Statutes: Powers of Attorney.[8] The durable power of attorney concept enables the surrogate designated by the patient to "do all acts necessary for maintaining the customary standard of living of the principal," including providing "medical, dental and surgical care, hospitalization and custodial care for the principal, spouse, and/or children." A durable power of attorney is superior to the usual power of attorney, since the latter usually lapses when the person granting it becomes incompetent. Thus, the usual power of attorney is of little legal merit in medical treatment decisions for incompetent patients. By contrast, the provisions of the durable power of attorney allow it to become effective or to remain in effect during incompetency. Also, the incompetency need not be determined in court if the document specifies another procedure.[5, 6]

A less formal way of capturing the patient's wishes about long-term care is to request that the patient simply write a letter of "instructions to my physician" (E. A. Stead, Jr., M.D., personal communication). In this letter, the patient can express his or her wishes about ways in which he might wish to be cared for in the event of various outcomes based on the patient's current or anticipated medical problems. Obviously, it would behoove the physician to note the receipt of such a document in his own records and to include it in the medical record any time the patient is admitted or transferred to a new medical institution, including a nursing home.

Regardless of the form of these advance directives, it is important to recognize that the process of discussing these outcomes may be as important as the decisions and the outcomes. Open, frank discussions of various treatment/care options between the physician and the patient and family increase the likelihood that good decisions will be made and that good outcomes will be achieved. The best outcomes and decisions are those in which everyone feels mutually satisfied.

Incorporating Patient Wishes into Nursing Home Plans

Ideally, a physician who has enjoyed a professional relationship of substantial duration with an older patient should continue to provide care even after that patient enters a nursing home. According to Kapp:[9]

"Physicians who admit individuals to nursing homes should understand both their own legal and ethical responsibilities and those obligations of the nursing home to which the patient is admitted. Personal physicians, nursing home administrators, and medical directors, must work together to insure that their separate and mutual duties are being carried to the ultimate betterment of the resident. Where the nursing home already has a policy in effect regarding its expectations and requirements concerning admitting physicians, the admitting physicians should be aware of the policy, scrupulously obey it, and offer to assist in amending portions that are unreasonable or otherwise ill-advised. The physician should also strive to exert influence to encourage his or her students and peers to act similarly regarding their own nursing home patients. Where the nursing home to which the physician sends patients has not yet adopted a policy in this area, the physician practicing in the community should help to design a policy that reflects his or her legitimate needs and concerns, while adequately protecting the rights of the residents."

Physicians with patients in nursing homes should also be aware that the nursing homes themselves are increasingly being advised to adopt policies and procedures that specify the mechanisms for decision making in their institutions. These include a description of the roles and responsibilities of the physician and mechanisms for reviewing these decisions.

"Overall, facility policies concerning medical decision making generally, and 'life and death' decision making in particular, should be clear, explicit, and consistently applied. While the professionals involved in the actual decision making process may understand the reasoning involved, many staff members will need special help in understanding why and how these decisions are made. Facility policy should be flexible enough to account for individual circumstances and staff should be given sufficient information to understand the differences. Direct care staff, in particular, will need careful training and continued support to carry out 'comfort measures only' or supportive care plans. Physician orders that include detailed components of a supportive care plan for the individual resident should be required by the facility's procedures. Under no circumstances should it be possible to infer that the resident for whom supportive care only is appropriate has been abandoned by the health care team or the facility."[5]

Obviously, both the patient and the family, as well as the physician will feel much more comfortable if the nursing home provides vigorous supportive care for the patient rather than simply orders for "do not resuscitate," "do not intubate," etc. The physician (and/or nursing home) should supply a list of specific measures, in the form of orders, that clearly delineates the kind of care measures that are needed by the patient and are always medically appropriate. As noted by Lynn[10] these supportive orders should include consideration of symptom control, pain control (when necessary), mental function, gastrointestinal symptoms (including anorexia, dysphasia, nausea, vomiting, constipation, diarrhea), skin problems (such as decubitus ulcers, fistulas, sinuses), fever, weakness, respiratory symptoms. Also, the management of bereavement of the patient, family and staff should also be given consideration in these orders. If all of these orders are attended to, neither the patient nor the family should feel abandoned.

As an additional measure, both the attending physicians and the administrators of nursing homes should consider the establishment of advisory committees to prevent biased treatment regimens from being established by physicians, nurses, or administrators.[5] Attempts should be made to involve the residents of the nursing home in general policy issues whenever competent patients can be brought into such discussions. With regard to day-to-day decisions, these should probably be reviewed by a group of individuals who come from a broad-based perspective, both within the institution and from the community. Thus, lawyers, ministers, physicians, and other individuals with an interest in the broad prospectus of patient care should be available to help physicians and families review management decisions in which some conflict may arise.

Other Ethical Issues

Implementation of these policies will not be easy. Good treatment will require individualization of care plans. These care plans must meet the needs of the patient and family. However, individualization challenges (and sometimes negates) the equitable use of scarce resources such as nursing home personnel, services, and available dollars.

Good support measures for patients who are truly failing may mean only "decent minimum of care."[10] However, this may be truly caring care in much the same way that Hospice provides care for the terminally ill in their own homes. It may be much more appropriate to substitute an LPN instead of an RN when personal care is needed rather than high technology. Nevertheless, the physicians and nursing home personnel must be careful not to economize for one patient at the expense of others. When it is determined that life is no longer meaningful for a given patient, it would be reasonable to withhold or restrict treatment to save funds. However, this would be ethical in the realm of patient care only so long as the health care professionals retain control of these funds and have alternate ways of spending the money. It would be unreasonable and unethical for the government to reclaim the money only to use it for non-health care purposes (C. K. Cassell, personal communication).

For physicians to continue to be involved with the care of their patients in nursing homes, it is important that they be appropriately reimbursed for the time and effort spent there. It is recognized that reimbursement from Medicare and Medicaid (the latter funds approximately 65% of all nursing home residents in North Carolina) is usually slow and sometimes contentious. Nevertheless, it is possible to bill Medicaid and Medicare for services rendered at intervals more frequent than once a month. To be eligible for reimbursement, the physician must document the problem(s) for which care is being given and use procedure codes that are readily recognized and accepted by Medicaid and Medicare reimbursement agents. Appendix A shows responses to questions I posed to EDS Federal regarding Medicaid reimbursement for physician services for nursing home care in May 1985. I believe that these answers will be very helpful to any physician who provides care for nursing home patients. In particular, I would stress that the physician (1) document (both in the medical record and in the bill to Medicaid/Medicare) the reason for the visit and (2) select a procedure code from the 903 series that would be appropriate for the nature of the problem and the amount of time spent with the patient.

Conclusion

Appropriate medical care for nursing home residents remains a major medical, ethical, moral, and economic challenge for the practicing physician. I believe that caring physicians can provide important leadership for nursing homes and their administrators and staff, as well as comfort to patients and their families. This requires sagacious consideration of care needs and wise investment of time with these patients. Through some consolidated effort and planning, many important advances can be made in the care of these patients at little additional cost and relatively small expenditure of time by the physician. With a modest increase in the amount of time spent communicating effectively with patients and families particularly before events become critical, by encouraging the use of advance directives, and by documenting these efforts, physicians will be making important contributions to the health care of frail patients and their families.

Appendix A

Responses to questions directed to EDS Federal regarding Medicaid reimbursement for physicians services for nursing home care.

1. How are physicians reimbursed for nursing home care?

Medicaid will pay per visit per CPT code, using codes 90300-90370 found in the CPT code book. Physicians are reimbursed at 100% of the billed amount or the amount allowed for the particular CPT code on a fee schedule based on the doctor's specialty, whichever is less.

2. How often are physicians required to visit nursing home patients?

For Skilled Nursing Facility (SNF) Patients:

Medicaid patients must be initially certified by a physician at the time of admission, or if an individual applies for assistance while in an SNF, before the Medicaid Agency authorizes payment. Physician recertification must be made at 30, 60 and 90 days after admission and every 60 days thereafter.

The physician is required to visit and write a progress note at least every 30 days. He/She is also required to review and renew orders every 30 days. After the first 90 days the physician can request approval of an alternate visit schedule from DMA/Utilization Control Section. If the patient's condition does not require physician visits every 30 days and it is approved, the alternate schedule cannot exceed 60 days between visits.

Each Medicaid patient must be reviewed by the Utilization Review Committee every 30 days from the day of admission up to the first 90 days and every 90 days thereafter for as long as the patient remains at the skilled nursing level of care. Readmission to the same level of care after hospitalization would start the review process over again.

For Intermediate Care Facility (ICF) Patients:

Medicaid patients must be initially certified by a physician at the time of admission, or if an individual applies for assistance while in an ICF, before the Medicaid Agency authorizes payment. Physician recertification must be made at 12, 18 and 24 months after admission and annually thereafter.

The Intermediate Care Facility's Utilization Review Plan must provide for a review of each recipient's need for continued stay at the ICF level of care at least every six months (180 days), for as long as the patient remains at the ICF level of care.

3. How ill must a patient be in order to qualify for the nursing home care?

Skilled Nursing Care

Skilled nursing services, as ordered by a physician, must be required and provided on a 24 hour basis, seven days a week.

If a patient's condition is such that it requires observation and assessment by technical or other professional personnel (licensed medical personnel such as a licensed practical nurse, physician assistant, etc.) to identify or evaluate the patient's need for possible modification of his/her treatment plan and the initiation of additional medical procedures until his/her condition is stabilized, the service is at the skilled level of care. These services must be documented by physicians' orders, progress notes, nurses' notes and/or therapists' notes.

In cases where the use of technical or professional personnel (licensed medical personnel) is necessary to teach a patient self-maintenance, such teaching services would constitute skilled services. Training programs of longer than two months will be considered appropriate for the intermediate level unless exceptional circumstances are present and fully documented by a physician.

The development, management and evaluation of a patient care plan based on physicians' orders constitutes skilled services when the patient's serious, unstable and/or deteriorating physical or mental condition (such as development management and evaluation) necessitates involvement of technical or professional personnel (licensed medical personnel) to meet his needs, promote his recovery and actuate his medical safety. Complications and special services involved must be fully documented by the physician's orders, progress notes, nurses' notes and/or therapists' notes.

"Total care," which is care given primarily by aides to assist in the activities of daily living, does not constitute skilled nursing care.

Intermediate Level of Care Criteria

The determination of the differences between skilled and intermediate levels of care is based upon the patient's condition, along with the complexity and range of medical and health related services required by the patient on a daily basis. The provision of room, food, laundry and supervision of activities of daily living do not, in any way, qualify as intermediate care.

Intermediate nursing care includes care for patients with long term illnesses or disabilities which are relatively stable and/or care for patients nearing recovery and discharge, who continue to require some professional medical and/or nursing supervision and attention. Intermediate care services encompass a range of services from those below skilled level services to those above room and board.

Intermediate services require some professional supervision but may be performed by properly trained non-professional personnel. A licensed nurse is required on an 8-hour daily basis for general observation and supervision, but most of the patients' requirements can be met by an attendant.

Intermediate care includes room, food, laundry, professional supervision of activities for protection and safety along with combinations of (1) assistance with ambulation, including getting in and out of bed; (2) assistance with general bathing, hygiene, dressing and eating; (3) provision and supervision of special diets; (4) provision and supervision of medications; and (5) provision and supervision of restorative measures.

4. How often can bills be submitted to Medicaid for services rendered to nursing home patients?

Charges can be submitted as often as the doctor sees the patient. The doctor may charge for any visit to the patient as long as the encounter is medically justified.

5. If the physician must see a patient more than once per month, will he/she be able to be reimbursed for each visit?

As long as it is medically justifiable that the patient be seen more than once per month, Medicaid will cover the visit; however, the degree of illness warranting additional visits must be indicated by the diagnosis code.

6. Please distinguish between a routine visit and a visit for a new or acute problem that develops that requires additional care not otherwise handled on routine visits.

If a physician is seeing a new or established patient for the initial care of a new or acute problem, he may select a procedure code from 90300, 90315 or 90320. For any follow-up care on that initial care, the appropriate code may be selected from 90340-90370.

7. Please give your definition of "ambulatory patient."

Ambulatory is considered not to be bedridden. For the purposes of whether Medicaid will pay for a nursing home visit for a patient who, even though he/she has physical limitations, can be transported to the office, Medicaid will pay for a nursing home visit if the visit is medically justified.

Notes:

If the physician wishes, skilled nursing facilities and intermediate care facilities can arrange with Medicare to have payments for contracted physicians' services to individual patients paid to the facility instead of the physician providing the service.

In order for Medicaid payment to be made to the facility for straight Medicaid claims or for Medicare/Medicaid crossover claims, the facility must request a special provider number for this purpose. The request for the physician nursing home staff provider number must be made in writing to DMA and must contain signed statements from the physicians involved relinquishing any payment for these services to the nursing home. Copies of the contracts with the physicians involved must be included.

After the provider number is assigned, the facility may bill for any visit the contracted provider makes to the home.

Reimbursement will be determined by the usual, customary and reasonable charge (as established by Medicare) of each physician.

The physician service claim form, Health Insurance Claim Form (HCFA-1500) must be used by nursing homes when billing for physician services.

As always, when filing for services covered by both Medicare and Medicaid, follow billing procedures established by Medicare. On crossover claims, Medicaid will pay the coinsurance/deductible determined by the Medicare carrier.

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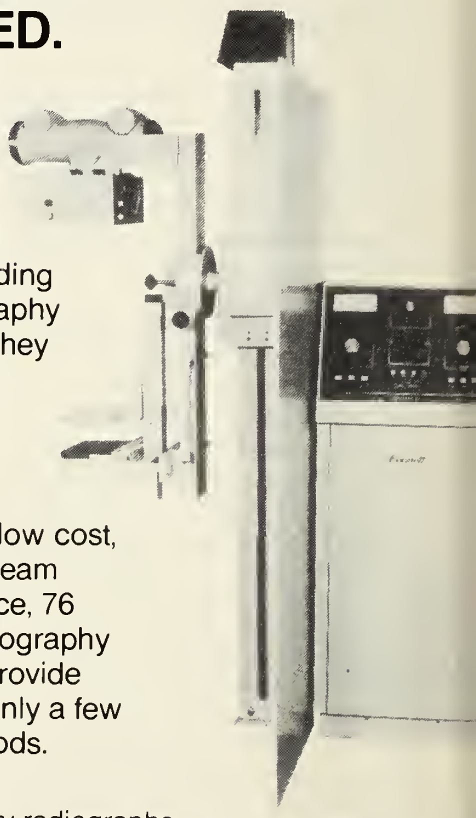

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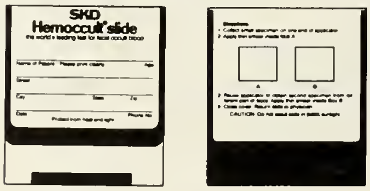
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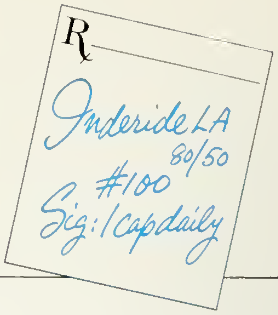

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CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated, and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or propranolol should be discontinued (gradually if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored In addition, when propranolol is prescribed for angina pectoris, the patients should be cautioned against interruption or cessation of therapy without the physician's advice If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure

Hydrochlorothiazide:

Thiazides should be used with caution in severe renal disease In patients with renal disease thiazides may precipitate azotemia In patients with impaired renal function, cumulative effects of the drug may develop

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma

Thiazides may add to or potentiate the action of other antihypertensive drugs Potentiation occurs with ganglionic or peripheral adrenergic-blocking drugs

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported

PRECAUTIONS

Propranolol hydrochloride (INDERAL®):

GENERAL Propranolol should be used with caution in patients with impaired hepatic or renal function Propranolol is not indicated for the treatment of hypertensive emergencies

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that propranolol may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

CLINICAL LABORATORY TESTS Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs, such as reserpine, should be closely observed if propranolol is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies, in both rats and mice employing doses up to 150 mg/kg/day there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

PREGNANCY Pregnancy Category C Propranolol has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximal recommended human dose There are no adequate and well-controlled studies in pregnant women Propranolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

NURSING MOTHERS Propranolol is excreted in human milk Caution should be exercised when propranolol is administered to a nursing mother

PEDIATRIC USE Safety and effectiveness in children have not been established

Hydrochlorothiazide:

GENERAL Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance namely Hyponatremia hypochloremic alkalosis, and hypokalemia Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids Medication such as digitalis may also influence serum electrolytes Warning signs irrespective of cause are Dryness of mouth, thirst weakness, lethargy drowsiness restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH

Interference with adequate oral electrolyte intake will also contribute to hypokalemia Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effect of digitalis (eg increased ventricular irritability) Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content

Any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver or renal disease) Dilutional hyponatremia may occur in edematous patients in hot weather, appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening In actual salt depletion appropriate replacement is the therapy of choice

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy

Insulin requirements in diabetic patients may be increased decreased or unchanged Diabetes mellitus which has been latent may become manifest during thiazide administration

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy

Thiazides may decrease serum PBI levels without signs of thyroid disturbance

Calcium excretion is decreased by thiazides Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy The common complications of hyperparathyroidism, such as renal lithiasis bone resorption, and peptic ulceration have not been seen Thiazides should be discontinued before carrying out tests for parathyroid function

DRUG INTERACTIONS Thiazide drugs may increase the responsiveness to tubocurarine

The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient Thiazides may decrease arterial responsiveness to norepinephrine This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use

PREGNANCY Pregnancy Category C Thiazides cross the placental barrier and appear in cord blood The use of thiazides in pregnancy requires that the anticipated benefit be weighed against possible hazards to the fetus These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult

NURSING MOTHERS Thiazides appear in human milk If use of the drug is deemed essential, the patient should stop nursing

PEDIATRIC USE Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Propranolol hydrochloride (INDERAL®):

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular Bradycardia, congestive heart failure, intensification of AV block, hypotension paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System Lightheadedness, mental depression manifested by insomnia, lassitude weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal Nausea vomiting, epigastric distress, abdominal cramping diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory Bronchospasm

Hematologic Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

Hydrochlorothiazide:

Gastrointestinal Anorexia gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis

Central Nervous System Dizziness, vertigo, paresthesias, headache, xanthopsia

Hematologic Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia

Cardiovascular Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics)

Hypersensitivity Purpura photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever respiratory distress, including pneumonitis, anaphylactic reactions

Other Hyperglycemia, glycosuria, hyperuricemia muscle spasm; weakness, restlessness, transient blurred vision

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn

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TOXIC ENCOUNTERS

A Bit on the Wilde Side: MDMA Abuse

Ronald B. Mack, M.D.

• *MDMA is a "designer" drug that would have appealed to a pleasure-seeking Oscar Wilde.*

THESE days a famous literary person with outrageous behavior and eccentric costume would be chronicled on the Donahue program and Johnny Carson show and people would probably be amused and intrigued but not surprised. Strange behavior no longer shocks in this age of adult "show and tell." But in the Victorian Age, non-conformity could land you in the slammer pounding "big ones into little ones." Such was the case of the infamous Oscar Wilde. We are not talking ancient history; my father was 5 years old when *this* gentleman of letters died.

The Victorian Age may not have been a fun time to live unless you were very conservative. Victoria became Queen of England in 1837 when she was a mere lass and her prior schooling consisted primarily of learning the "proper way" to conduct herself. Unfortunately she was not given the opportunity to have a more liberal education; this gave her a rather narrow outlook on the world, i.e., a Victorian perspective of what was going on. The standards of behavior in the Queen's time were extremely strict and if you broke the moral rules you became an outcast. It did not help when the love of Victoria's life, Prince Albert (the father of her nine children), died suddenly leaving her a disconsolate widow. For the next forty years of her life she mourned him, including dressing like a widow. Into this stuffy, rigid milieu enters Oscar Wilde whose evening dress consisted of knee breeches (worse than the corduroy knickers we had to wear in my day), black silk stockings, a velvet coat, a silk shirt and a large bow tie topped off by a large sunflower in his buttonhole. How long would he have lasted in your neighborhood? On the streets of Chicago, he would have had a T½ (half-life) of 37 minutes.

I could find no evidence that this young rebel took drugs on a regular basis (licit or otherwise), but he did have the ability to consume large quantities of ethanol on a regular basis. One of the drugs I am sure he would have loved is MDMA, AKA "Ecstasy," "Adam," MDM or 3,4-methylenedioxymethamphetamine. Why would he have liked this drug, you ask? I'll tell you why — it makes you feel good, and Oscar Wilde liked to feel good. Here, let him tell you himself. "I let myself be lured into long spells of senseless and sensual ease . . . I took pleasure where it pleased me and passed on . . . I filled my life to the very brim with pleasure, as one might fill a cup to the very brim with wine" (or decaffeinated instant coffee).

MDMA is known in the trade as a "designer" drug. "Designer" drugs refer to chemicals prepared to produce a preselected physical effect — a "feel good." The term currently also implies a new "mind-bender" produced chemically by manipulating an existing drug so as to produce a "new" preparation that is not illegal. As you can see, "designer" drugs are like "designer" clothes. I wear them, don't you? Just check my labels, Buster — *Il Sears, La J.C. Penney* or when I am feeling extravagant *Le K-Mart.*

MDMA has been available since 1914. It was briefly popular during the 1960s when it seems almost anything was tried for its psychedelic effects, e.g., smoking banana peels, sniffing Italian red peppers, etc. It seems to have become quite popular recently and prescribed legally by some in our profession, but as we shall see momentarily its legal status has been rescinded. This drug is a synthetic compound derived from one of the essential oils in nutmeg — myristicine. It differs from the psychedelic MDA (3,4-methylenedioxyamphetamine) only by the presence of a methoxyl group in the molecule. Pharmacologically, MDMA produces clinical effects similar to both mescaline and amphetamines. Mescaline, you may recall, can produce rather remarkable vivid perceptual distortions, more visual than auditory; time is distorted, as are body image, space, and so on. A real fun time! In low doses the psychotropic effects are said to be similar to other hallucinogens, MDA, peyote, etc., but in larger doses it acts like LSD.

The users of "Ecstasy" exclaim that the chemical relaxes inhibitions and increases effective communication and sex (spare me from another aphrodesiac; none of them work, except of course shrimp marinara with cannoli for dessert). Until recently, you could have MDMA prescribed if your psychiatrist believed in it, but of course you still can buy it on the street. When purchased on the street, if it's the real stuff, you can buy it in gelatin capsules or as a powder to be mixed with fruit juice. It sells for about $10 to $30 for 100 mg. Therapists who endorse this drug allege that with controlled dosages it can "neutralize emotional defenses," help the patients get in touch with their feelings (whatever that means; I'm sick of that phrase!! Will someone please think up a new one!!). Many satisfied customers allege that with usual doses one experiences a feeling of joy and well-being without the hallucinatory dissociation from reality.

From the Department of Pediatrics, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem 27103.

Speaking of "Ecstasy," do any of you remember the famous movie of that name with the ever-popular star Hedy Lamarr? When I was a young lad this was an adult's-only film (no "R" rating or "X" rating in those days). What a fuss about nothing — the movie shows Hedy, barefoot all over, swimming for a few nanoseconds!! For shame!! My 5-year-old grandson, Jeb, sees more nudity than that when he goes to the swimming pool or turns on cable TV.

Now, what did Oscar Wilde do to offend public morals and land in jail? In case you forgot, this dude was married and fathered two sons but he also indulged in other sexual outlets that were not publicly (or is it not pubicly) accepted. Hard to believe, but the Marquis of Queensberry (the boxing rules expert) who advocated not hitting below the belt literally did so figuratively by accusing our Wilde man of being a card-carrying homosexual. Our anti-hero sued the Marquis for libel (bad move). Queensberry's lawyers found plenty of evidence and witnesses to prove that Oscar was in fact gay. Oscar Wilde was subsequently indicted for "committing acts of gross indecency with other male persons." He was found guilty and sentenced to two years in prison at hard labor. In prison he wrote an incredible letter — very, very long and moving called *De Profoundis* — that is one of the most explicit examples of a person's feelings that I have ever read. In 1897 he was released from prison and wrote the famous poem, *The Ballad of Reading Gaol* — "And all men kill the thing they love, By all let this be heard, Some do it with a bitter look, Some with a flattering word, The coward does it with a kiss, The brave man with a sword!"

Well, back to "feeling good." If you get too much MDMA or use it for prolonged periods you can get amphetamine-like side effects which include tachycardia, cardiac arrhythmias, hypertension, panic attacks, remarkable diaphoresis, diplopia, bruxism and something more weird: involuntary teeth clenching. The FDA has recently cried "Hold, Enough" and placed an emergency ban on the use of MDMA as of July 1, 1985. This drug was placed in Schedule I of the Controlled Substances Act ("has high abuse potential, no acceptable medical use and no accepted safety for use"). The Drug Enforcement Administration cites abuse of MDMA as a "nationwide problem." This restriction may cut down on some of the "legitimate" use of this drug by some psychiatrists but certainly the illicit manufacture, distribution and use will flourish. I must admit that I have not seen a case of MDMA abuse. We did have a patient who said his family burned all the umbilical cord stumps of the children born to them to prevent enuresis. (He admitted upon questioning to two facts: (1) the cord was not still attached to the baby when burned; (2) it prevented bedwetting 100% of the time.)

The management of an adverse reaction to MDMA would seem to be very symptomatic, i.e., monitoring heart rate and rhythm and blood pressure and using drugs like propranolol for worrisome tachycardia and severe hypertension with nitroprusside or phentolamine. Maybe descretion is the better part of valor here. If any of your patients feel that they need this drug to stay afloat, suggest instead cannoli and a cup of expresso. That ought to do it. It works for me!!

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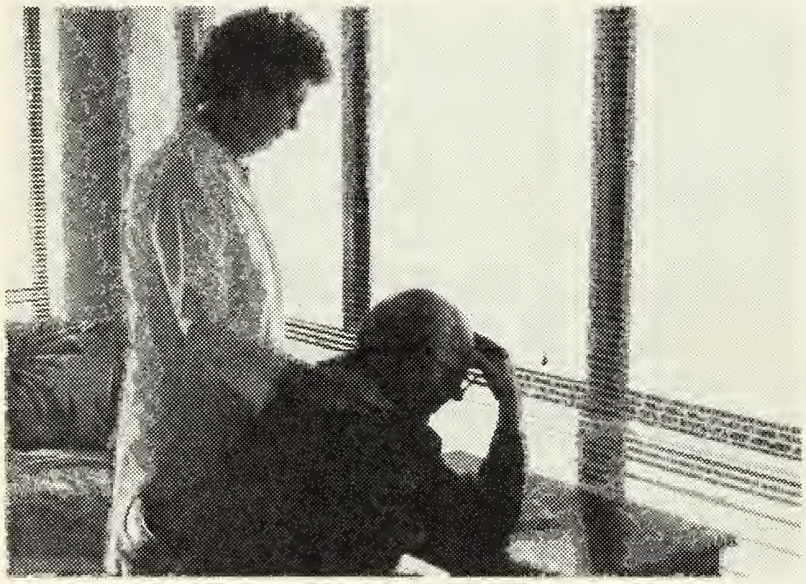

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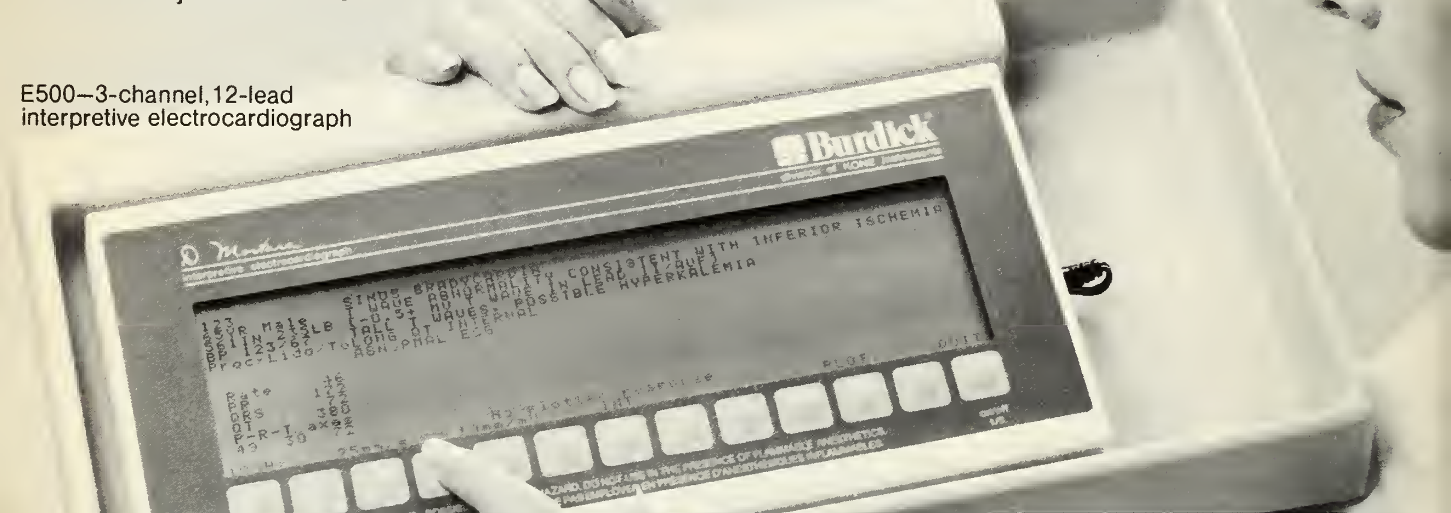

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The Rankin Clinical Research Unit of Duke University Medical Center Commemorates 25th Anniversary

Edward L. C. Pritchett, M.D. and William G. Anlyan, M.D.

- *A recollection of the first 25 years of Duke's Rankin CRU.*

THE Rankin Clinical Research Unit of Duke University Medical Center commemorates the 25th anniversary of its founding this month.[1] The Unit's lineage is the specialized research hospital wards that were an important innovation of American medicine in the early 20th century. Prior to that time, faculty members in American medical schools commonly maintained offices for private practice and supported themselves with the income from this practice. Remuneration for teaching and research was meager. With the establishment of full-time faculties around the turn of the century, physician time was more concentrated in the medical school hospitals.

The first dedicated research ward was an entire hospital, the Hospital of the Rockefeller Institute, which opened in 1908. Rufus Cole came from the Johns Hopkins Hospital to be its first director. Dr. Cole was interested in lobar pneumonia, and the Hospital of the Rockefeller Institute developed a strong theme of microbiology in its early years. Similarly, Eugene Dubois founded a research ward at Bellevue Hospital in 1913. In 1925 James Howard Means opened Ward 4 of the Massachusetts General Hospital for clinical research. Other metabolic units opened in 1935 at the University of Michigan and at the Mayo Clinic.

In 1953 the National Institutes of Health (NIH) opened its clinical center in Bethesda, Maryland. The initial staff was recruited from the research wards at the University of Michigan, the Mayo Clinic, and the Massachusetts General Hospital. By the late 1950s the NIH began to discuss the concept of extramural clinical research centers. Funds to establish twelve centers were appropriated by Congress in 1960, and applications were accepted by the Division of General Medical Sciences.

The application from Duke University Medical Center was assigned grant number OG-5; Frank L. Engel was the principal investigator (see cover photo). Like many early Duke medical faculty, Dr. Engel was tied to Johns Hopkins, having received his M.D. degree there in 1938. He came to Duke in 1947, having been in the interim at Woods Hole in Massachusetts, Mount Sinai Hospital in New York, Yale University, and Emory University. Dr. Engel wrote proposal OG-5, "To Establish a General Clinical Research Center." In addition to being principal investigator, Dr. Engel served as Chairman of the Center Advisory Committee and as Program Director, jobs that are now divided among three individuals. The application indicated that the medical center intended to recruit a permanent director from the outside. The original advisory committee consisted of the chairmen of the departments of Biochemistry, Medicine, Pediatrics, Psychiatry, and Surgery. The application proposed putting the center in Strudwick Ward, a vacant area requiring minimal renovation before it could be used. A permanent home for the center awaited construction of a new addition to the medical center, The Clinical Research Building.

The application opened with the statement, "The Clinical Research Center is conceived as a facility in which patients may be hospitalized for controlled observation and study in relation to the diverse programs of clinical research in progress or contemplated at the Duke University Medical Center." Dr. Engel anticipated that investigators would fall into five large categories: Endocrinology and Metabolism; Cancer and Chemotherapy; Cardiovascular, Pulmonary and Renal Medicine; Behavioral Medicine; and Rheumatology. He recognized that both adult and pediatric patients would be studied in each group. Among the initial cohort of investigators was James Wyngaarden, who proposed to study "Purine Metabolism in Gout." Dr. Wyngaarden would later become director of the National Institutes of Health. Another young investigator was William Anlyan, a general surgeon, who proposed to study "Etiology and Treatment of Thromboembolic Disorders." A few years later Dr. Anlyan would become dean of the medical school and principal investigator of the General Clinical Research Center grant.

The initial grant application was submitted in January 1960. In April Edgar Lee, Jr. (Chief, *Ad hoc* Section, Clinical Research Facilities, Division of General Medical Sciences) sent a revised budget to Dr. Engel indicating an intention to fund the application. However, Dr. Lee's letter closed with the traditional NIH warning, "this letter does

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From the Department of Medicine, Duke University Medical Center, Durham 27710.

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not constitute a formal statement of award.'' Drs. Engel and Lee continued to correspond throughout the summer. Dr. Engel continuously requested reassurance that the grant would be funded, and Dr. Lee attempted to provide that reassurance, without abandoning the stated caveat. On October 17, 1960 Dr. Engel received a telegram stating ''Processing of award for clinical research center in progress. What do you request as initial payment which may not exceed $100,000?''

Apparently the initial grant, OG-5, was funded based solely on the written application. At the present time, the NIH customarily visits institutions applying for or renewing large center-type grants. Investigators make scientific presentations at these ''site visits''; the site visitors inspect laboratory facilities and meet with institutional officials. Site visits become landmarks in the histories of large programs, and the NIH conducted them at Duke when the CRU applied for renewal in 1966, 1973, 1978, and 1983.

The October funding notice did not allow time for the proposed renovations before investigators were ready to begin admitting patients. Therefore, three beds on Welch Ward, a general pediatric ward, were dedicated to the center, which locally was referred to as The Clinical Research Unit (CRU); patients were admitted beginning December 1, 1960. Four additional beds for adult patients were opened on Osler Ward on February 19, 1961. During the second funding year seven beds for both adult and pediatric patients were occupied on Welch Ward, and the unit achieved a true geographic identity. Later that year an additional eight beds were opened, bringing the total number to 15. By that time construction of The Clinical Research Building was well underway. Unexpended funds for renovation actually were returned to the NIH.

James B. Sidbury, Jr. was recruited from the Department of Pediatrics at Johns Hopkins to be the first director of the unit in 1961. Dr. Sidbury was a native North Carolinian. He received his M.D. degree from Columbia University College of Physicians and Surgeons, and he was trained in both medicine and pediatrics, the latter at Johns Hopkins. He was an instructor at Emory University, a staff member of the Communicable Disease Center, and an assistant professor of pediatrics at Johns Hopkins before being recruited to Duke. He was appointed associate professor of pediatrics and Director of the CRU at Duke in 1961. His research interest was inborn errors of metabolism.

In May 1963 The Clinical Research Building opened (figure 1), and the CRU moved to its permanent home, named Rankin Ward for Watson Rankin, the distinguished physician who had been in charge of the Hospital Section of the Duke Endowment. The new unit contained seventeen beds in five single rooms and six double rooms. A special room with a one-way mirror window was designed for studies on psychiatric patients. A kitchen on the ward provided regular meal service as well as special diets for patients on metabolic protocols. Office and laboratory space for the director and a small core laboratory for sample handling were included. The Women's Auxiliary provided furniture for the patient lounge, including a television set (still an uncommon amenity at the time). The entire unit was air conditioned, an important improvement over other sections of Duke Hospital where the hot Carolina summers baked the wards.

By the mid-1960s administration of the Unit had assumed its contemporary form. At the NIH the Division of Research Resources had assumed responsibility for the General Clinical Research Centers program, and grant number OG-5 had been reassigned number RR-30. At Duke Dr. Anlyan was Dean of the Medical School and

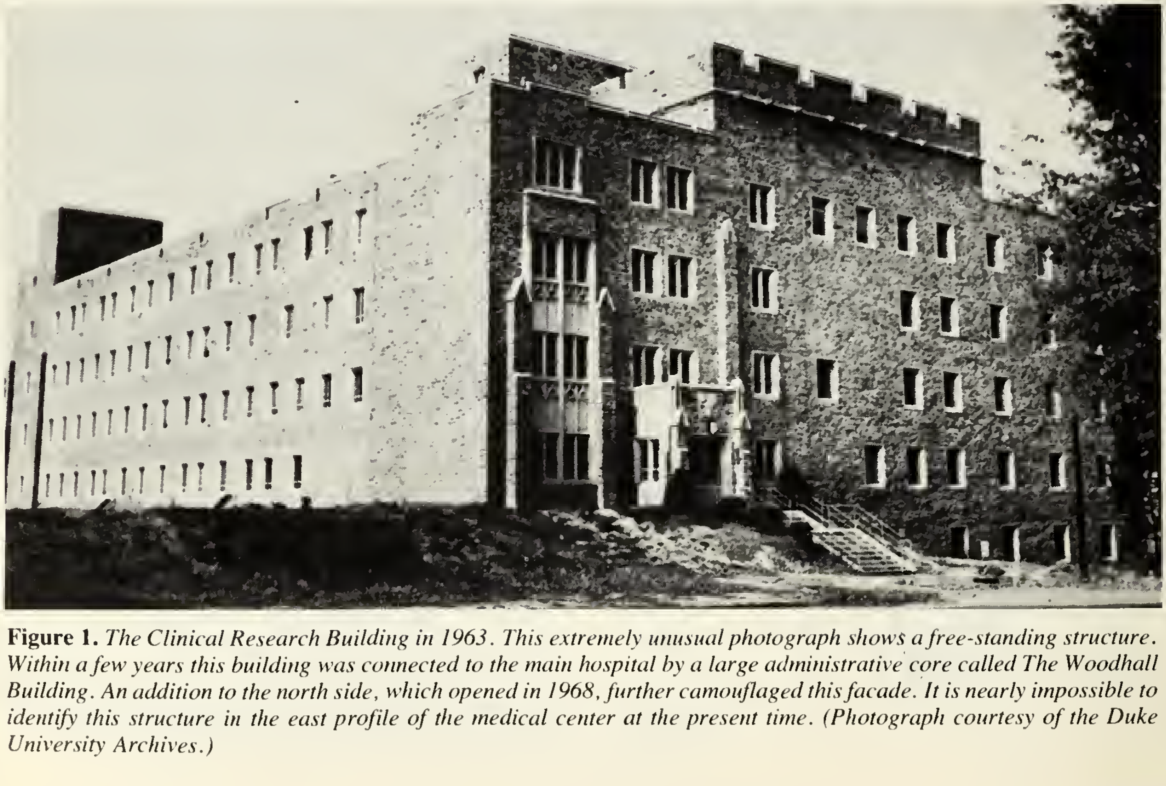

Figure 1. *The Clinical Research Building in 1963. This extremely unusual photograph shows a free-standing structure. Within a few years this building was connected to the main hospital by a large administrative core called The Woodhall Building. An addition to the north side, which opened in 1968, further camouflaged this facade. It is nearly impossible to identify this structure in the east profile of the medical center at the present time. (Photograph courtesy of the Duke University Archives.)*

Principal Investigator of the grant. Dr. Sidbury was Program Director; and Morton Bogdonoff was Chairman of the Advisory Committee, which included representatives from all clinical departments and some basic science departments. During its first several years of operation, the diversity of the unit predicted by Dr. Engel was demonstrated by the range of investigators using the most bed days. These included two pediatricians, Drs. Sidbury and Robert Stempfel; a cardiologist, Henry McIntosh; a neurosurgeon, Blaine Nashold; a gastroenterologist, Julian Ruffin; an endocrinologist, Harold Lebovitz; and a hematologist, Wayne Rundles. Training was an important theme. In 1966 there were 25 separate training grants active in the institution, and trainees from almost all of them rotated through the CRU.

In 1968 an addition to the north side of The Clinical Research Building opened and added one double room and two single rooms to the Unit. The single rooms were intended for patients requiring "intensive care unit" treatment, and both had the latest equipment for bedside electrocardiogram monitoring. About this time an isolation room with laminar air-flow control was built for neonatal patients with immune deficiency diseases.

Dr. Samuel Wells, a general surgeon, was appointed associate director of the Unit in 1972. Dr. Wells had received his M.D. degree from Emory University and then did two years of training in internal medicine at Johns Hopkins. He received additional training in general surgery and additional research experience at Washington University, Barnes Hospital, St. Louis; The National Cancer Institute; The Karolinska Institute, Stockholm; and Duke University before being appointed assistant professor of surgery at Duke in 1970. Dr. Wells used the CRU extensively as a site for studies of patients with medullary carcinoma of the thyroid gland, multiple-endocrine neoplasia type II, and parathyroid disorders.

When the renewal application was written in 1973, Drs. Sidbury, Nashold, and Lebovitz remained among the most active users. Drs. Stempfel and McIntosh had departed, and important new programs had emerged. Delford Stickel (general surgery) and J. Caulie Gunnells (nephrology) studied patients with renal diseases. Wendell Rosse (hematology) and John Tindall (dermatology) became major users, as did William Kelley, who studied abnormalities of purine metabolism. Rebecca Buckley developed a strong program studying immune deficiency diseases in children. Dr. Buckley's protocol #150, submitted in 1965, remains the longest continuously active protocol on the unit; and Dr. Buckley has the distinction of being the only investigator to present at three CRU site visits (in 1973, 1978, and 1983).

Dr. Sidbury departed in August 1976 to become scientific director of the child health program at the NIH, and Dr. Wells was appointed Director. During Dr. Wells' tenure as Director, the core laboratory was substantially expanded, and radioimmunoassays for parathormone, calcitonin, and cyclic adenosine monophosphate were installed along with atomic absorption spectrophotometric assays for calcium and magnesium. These assays serviced a burgeoning group of investigators interested in disorders of calcium metabolism. In addition to Dr. Wells, this group included George Leight (surgery); John Weinerth (urology); and Francis Neelon, Marc Drezner, and Kenneth Lyles (endocrinology).

In addition to expanding the core laboratory, the CLINFO computer system was acquired and a second isolation room was built by Dr. Wells. Drs. Lebovitz and Buckley continued to have large programs. Allen Roses (neurology) began a new large program studying patients with myotonic muscular dystrophy. Interdisciplinary research evolved between Dr. Wells (general surgery) and the associate director, Dr. Neelon (endocrinology), and between Drs. John Gallagher and Edward Pritchett (cardiology) and Will Sealy (thoracic surgery).

In 1981 Dr. Wells was appointed Professor and Chairman of the Department of Surgery at Washington University, St. Louis; Dr. Pritchett succeeded him as Director of the CRU. At that time Dr. Pritchett was collaborating with David Shand (pharmacology) in studying the clinical pharmacology of antiarrhythmic drugs and calcium channel blocking drugs. Drs. Buckley and Roses continued to be major users of unit resources; and Hugh Sampson, who had been trained by Dr. Buckley, was appointed associate director. Dr. Sampson studied patients with atopic eczema and food allergy in addition to sharing responsibility with Dr. Buckley for studying patients with immune deficiency diseases.

The composition of investigators using the CRU in the mid-1980s continued to confirm Dr. Engel's prediction of diversity and the tradition of collaboration between basic and clinical sciences. Ninety-one investigators with 110 academic departmental appointments were using the CRU. Clinical investigators were active from the departments of Medicine, Pediatrics, Surgery, Psychiatry, Obstetrics and Gynecology, Radiology, and Community and Family Medicine; and almost a quarter of the appointments were in basic science departments.

Acknowledgment

The authors appreciate the following individuals who lent their records and their recollections to us while we wrote this history: William Glitz, Mildred Engel Handleman, Leon Lack, June Perry, Eugene Stead, Jr., R. Wayne Rundles, James B. Sidbury, Jr., and Samuel Wells. We also acknowledge the contribution of the Duke University Archives (William King) and the Medical Center Archives (James Gifford).

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Features for Patients December 1985

CATARACT & LENS IMPLANT SURGERY

John V. Thomas, M.D.

When you are told that you have cataracts, it is natural to be concerned about your vision and uncertain of what will follow. My purpose in writing this booklet is to reassure you by describing what cataracts are, what lens implants are and how cataract surgery with lens implantation is done. I have tried to anticipate and answer some of the questions you may have and hope that this will serve you as a useful guide before and after cataract surgery.

From 100 Charles River Plaza, Boston, MA 02114. Illustration and design by Laurel L. Cook.

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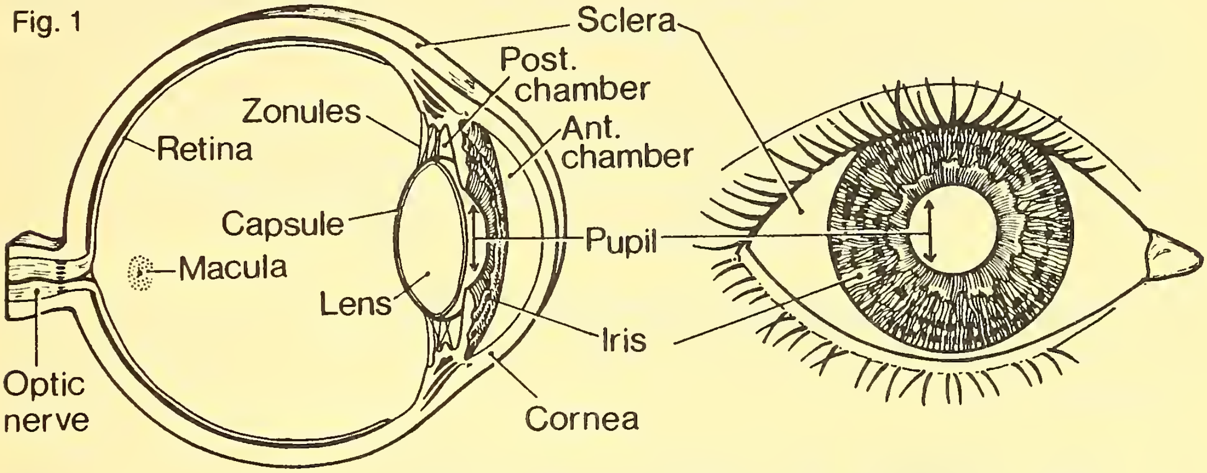
1 What is a cataract?

In order to understand what a cataract is, one needs to know a little bit about the eye and how it works. The eye is almost spherical in shape and contains within it a lens which is clear and colorless like glass (see Figure 1). The lens is slightly smaller than a lima bean and lies behind the iris. The iris is the part of the eye which makes a person blue eyed or brown eyed.

Fig. 1



The lens of the eye is surrounded by a thin, saran-wrap like membrane called the capsule (see Figure 1). The lens has the function of focusing light on the retina which is a light-sensitive lining inside the eye. The retina is connected to the optic nerve which in turn is connected to the brain. When light falls in the retina, visual messages are transmitted to the optic nerve and finally to the brain enabling us to see.

Normally, light passes through the clear cornea (the transparent dome-like structure in the front portion of the eye), through the pupil (which is the round opening formed by the iris) and through the colorless lens which focuses it on the retina (see Figure 2).

EYE WITH NORMAL LENS

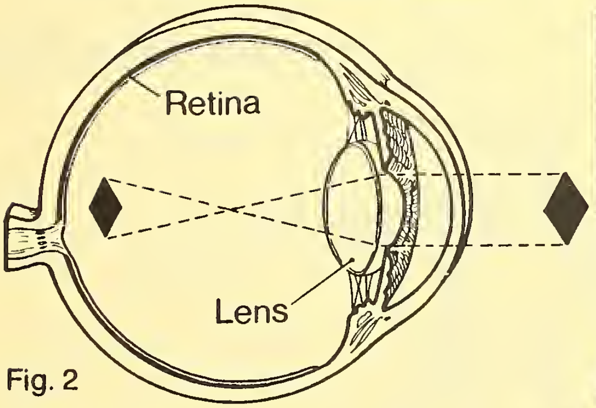


Fig. 2

EYE WITH CATARACT

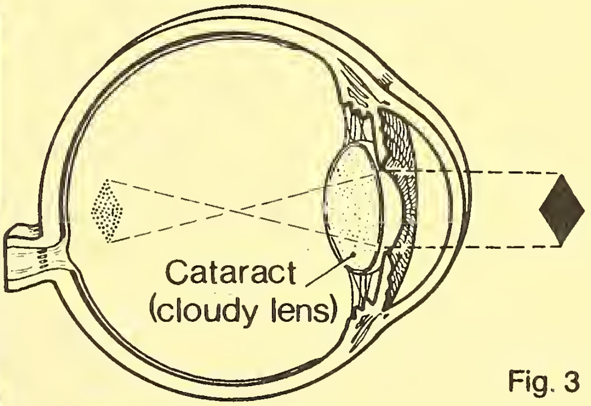


Fig. 3

When a colorless lens acquires color, becomes cloudy or slightly opaque, it is called a cataract. While a clear lens is able to let rays of light pass through itself, a cataract prevents light rays from passing through as they should. This causes a blurred image to fall on the retina and, as a result, causes a person to have blurred vision (see Figure 3).

A cataract is not a film over the eye. It is also not a growth or tumor. It does not spread from one eye to another like an infection. It develops independently in each eye, although both eyes are usually affected. One eye may acquire a cataract months or even years before the other eye does.

2 What causes a cataract?

Most cataracts are due to increasing age. Other less common causes are injuries to the eye, inflammation within the eye, certain types of medication, x-rays, and diseases such as diabetes.

Cataracts do not occur due to poor eating habits, smoking or drinking too much, or overusing your eyes. Having a cataract does not mean that the rest of your body is deteriorating and not in good shape. You can be very healthy and still have cataracts. Even babies are occasionally born with cataracts.

3 How many people have cataracts?

More than 50% of all Americans can expect to have cataracts by the time they are 65 years of age.

4 How rapidly do cataracts develop?

Cataracts usually develop slowly over many years or even decades although some may develop more rapidly.

5 Is visual loss from a cataract permanent?

No. Unlike certain other diseases of the eye, for example glaucoma, the vision lost from a cataract can be restored.

6 What are the symptoms of a cataract?

They can vary from person to person. Blurred vision or a dimming of vision is common. You may also have difficulty reading small print and driving at night.

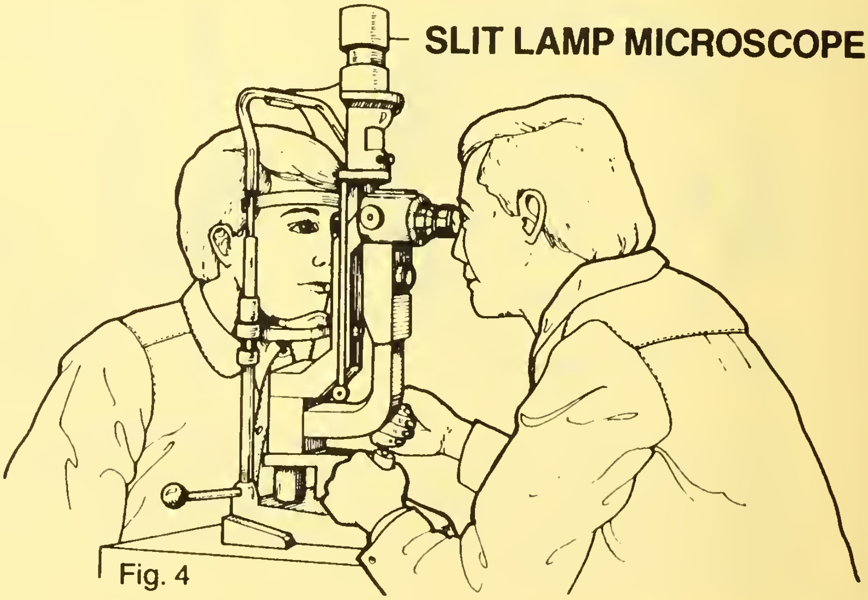


Fig. 4

7 How is a cataract diagnosed?

A diagnosis of a cataract is made by testing your vision and by looking at the lens within your eye with a slit lamp microscope (see Figure 4).

8 How is a cataract treated?

At first, a change in eyeglasses might help. Later, as the cataract advances, even changing glasses will not improve vision. At this point, the treatment is surgical.

Eye exercises, vitamins, or eye drops do not cure cataracts. A lot of research is being done to develop non-surgical methods of treatment and it is possible that in the future we may be able to stop the progression or prevent the occurrence of cataracts.

9 How successful is cataract surgery?

Very successful. 95% of people have improved vision after surgery.

10 Can a laser be used instead of surgery to remove a cataract?

No. A laser cannot be used to remove a cataract. The laser is often confused with an instrument called a phacoemulsifier, which uses high frequency sound waves to break up the cataract during surgical removal.

11 When will I be ready for cataract surgery?

You will know that you are ready when you have trouble seeing well enough to do things you must or would like to do. If, for instance, you wish to read and cannot read or wish to drive and cannot drive or if you feel unsafe walking or feel embarrassed by not recognizing friends on the street, you should consider surgery. On the other hand, if you have less than normal vision but are content with things as they are, the surgery can be postponed indefinitely, without harm.

Most cataract surgery is elective. Leaving a cataract in the eye almost never damages any other part of the eye. Allowing a cataract to progress does not compromise the vision you will get after surgery.

Because of new advances in surgical technique, it is no longer necessary to wait until a cataract is "ripe" or hardened. Before you decide to have cataract surgery, take the time to think it over and talk about it with family and friends.

12 Am I too old for cataract surgery?

No. Age by itself is not a factor in deciding whether or not to perform cataract surgery. General health, lifestyle and the medical condition of the eye are the important considerations.

As an example, if you are over eighty, in poor general health, and are sedentary, cataract surgery probably would not be necessary. If on the other hand, you are over eighty, healthy, alert and active, cataract surgery would probably be beneficial.

It is important to remember that with advanced age, the eye may develop disorders in addition to cataract that might limit vision, even if the cataract were removed. For example, macular degeneration which is an aging process in the macula (the part of the retina responsible for clear central vision that enables you to see small print) can prevent the restoration of good vision even after a cataract is removed.

13 What are the different ways in which cataracts are removed?

Basically, there are two ways in which a cataract can be removed. In both techniques, the eye is surgically opened.

1 In the "Intracapsular" technique, an enzyme is injected into the front portion of the eye which weakens the zonules (see Figure 1) which hold the lens in place. The entire cataract is then removed from the eye with a cold probe which is brought into contact with the lens capsule (see Figure 5). The probe freezes a portion of the cataract which then sticks to it and enables the surgeon to pull the entire cataract out of the eye. "Intracapsular" means inside the capsule and "intracapsular cataract extraction" means that the cataract is taken out while it is inside the capsule.

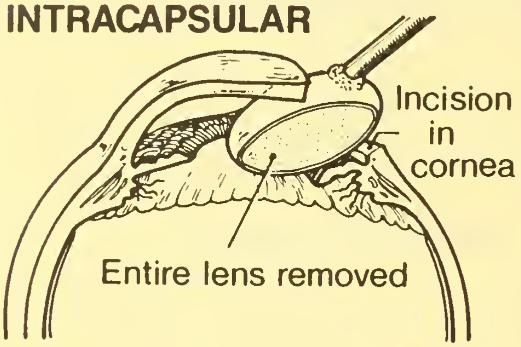


Fig. 5

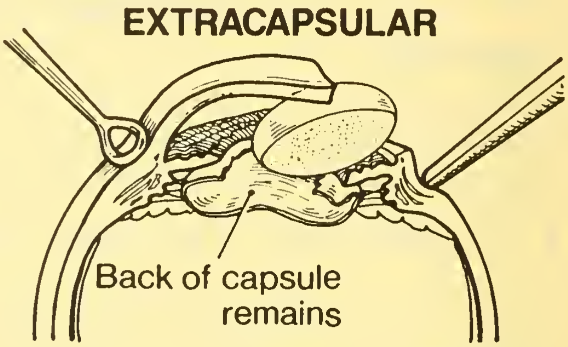


Fig. 6

2 In the "Extracapsular" technique, an opening is made in the front part of the lens capsule and the contents of the capsule are gently removed from the eye leaving an intact back capsule in the eye (see Figure 6). The capsule is clear and allows light to pass through normally. Advantages of leaving the back capsule in the eye are that it may help prevent retinal detachment and macular edema (swelling of the retina). A disadvantage of extracapsular extraction is that the back capsule in some eyes may become cloudy months or years after surgery and reduce a person's vision. However, with the use of a laser, vision can be restored by a painless procedure taking only a few minutes and done in your doctor's office. Phacoemulsification is a variation on the extracapsular technique in which a needle-like device producing high frequency sound waves is used to break up the cataract while at the same time sucking it out of the eye.

At present, it is generally thought that the extracapsular technique is the best way to remove a cataract. However, there are exceptions to this and your surgeon will decide which is best for your particular eye.

14 What is a lens implant?

A lens implant (intraocular lens or IOL) is a man-made, tiny, clear, plastic device which is placed inside the eye at the time the cataract is removed. It replaces the natural lens and remains permanently within the eye.

15 If I don't want an implant, how can my vision be restored after cataract surgery?

If an implant is not placed in the eye, cataract glasses or contact lenses are two options by which vision can be restored after surgery.

Although cataract glasses are a tried and true way to restore sight after surgery, they have several drawbacks (see Figure 7). They make things appear closer to you and about one-third larger than they really are. In addition, they may make objects seem curved and distort side vision so that to see things clearly to the left or right, you have to turn your head instead of just glancing in that direction. You may also have trouble doing simple things like putting a key in a lock or going up and down stairs. Driving can also be difficult. However, many people get along quite well with cataract glasses.

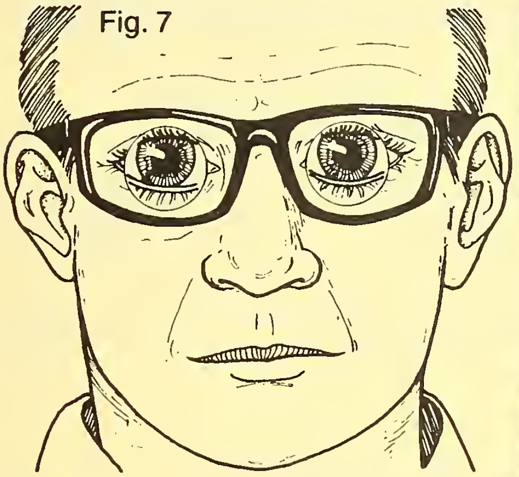


Fig. 7

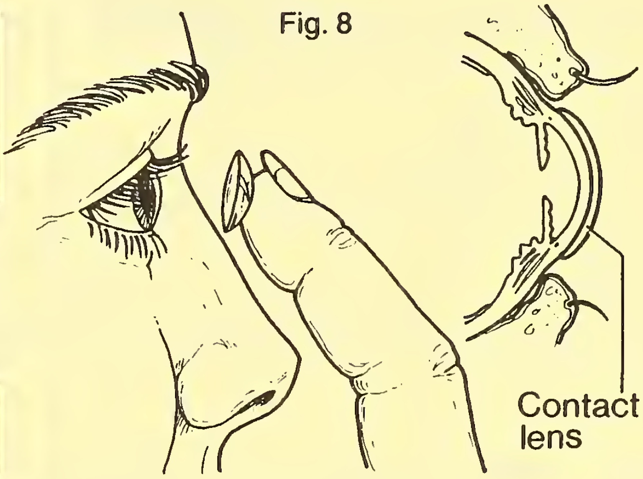


Fig. 8

Contact lenses provide more natural vision than do cataract glasses. Objects appear only slightly larger than they actually are, and side vision is more normal. However, contact lenses lie on the outer surface of the eye (see Figure 8) and most types have to be removed, cleaned and reinserted relatively frequently. Older people may find them somewhat difficult to handle.

Lens implants are optically superior to cataract eyeglasses. Vision with an implant is as close as possible to the normal vision you had with your own natural lens. Lens implants are also more convenient than contact lenses.

16 How long have lens implants been used?

The first lens implants were used over 30 years ago. More recently the design of implants has been improved and perfected and cataract surgery with lens implantation is now a common procedure.

17 How common is cataract surgery with lens implantation?

In 1983, 700,000 cataract extractions were performed in the United States. Over 500,000 or 70% of these patients received lens implants.

18 Are there different types of lens implants?

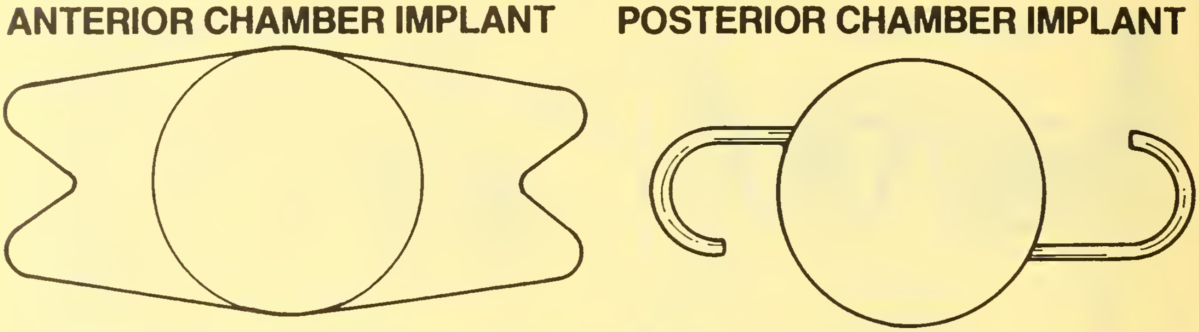
Yes. They come in various shapes and sizes, but basically, there are two types of implants which are in common use today: (see Figure 9)

1 Anterior chamber implants:

These implants are inserted into the anterior chamber of the eye which is the space between the iris and the cornea (see Figure 10). They are usually used when intracapsular cataract surgery is done.

2 Posterior chamber implants:

These implants are inserted into the posterior chamber which is the space behind the iris (see Figure 11). They are used when extracapsular cataract surgery is done. The back of the lens capsule that is left at the time of extracapsular cataract extraction provides a support for these implants.



These diagrams are much larger than actual size of implants.

Fig. 9

19 Which type of implant is best for me?

Although there has been an increase in the use of posterior chamber lens implants in recent years, your surgeon will use his judgment in deciding which type is best for your particular eye.

20 What is a "secondary implant?"

If a person has a cataract removed without lens implantation, his vision is corrected with cataract eyeglasses or a contact lens. If neither can be tolerated, it is possible to put an implant in the eye even years after the cataract is removed. In such an instance, the implant used is called a "secondary implant."

21 What type of testing do I have to go through before having cataract surgery with lens implantation?

The tests mentioned below are done in your ophthalmologist's office a few weeks before your cataract surgery. Your vision will be tested and the pressure in your eyes will be checked. Your pupil will be made larger with eyedrops so that the back of your eye can be checked thoroughly for diseases that can affect the success of the operation, such as diabetes and macular degeneration. You should remember that after dilation, your vision for reading will be blurred for a few hours. Also when you go into the sun light, the light may be very bright because more light is now entering the eye. So it is advisable to bring sunglasses with you.

The focusing power of the implant that will be appropriate for your eye is also calculated. To do this, the curvature of the cornea or front surface of your eye has to be measured using an instrument called a keratometer. This instrument does not touch the eye and the procedure is painless. The length of the eye from back to front is also measured using an ultrasound machine (see Figure 12). In this test the instrument touches your eye but there is no pain because your eye is numb from an anesthetic eye drop placed in it before the test.

It is also important to have your family doctor or internist check you and certify that you are healthy enough to go through eye surgery.

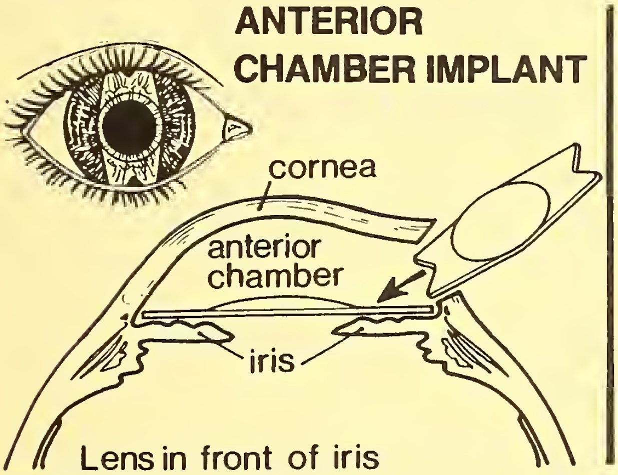


Fig. 10

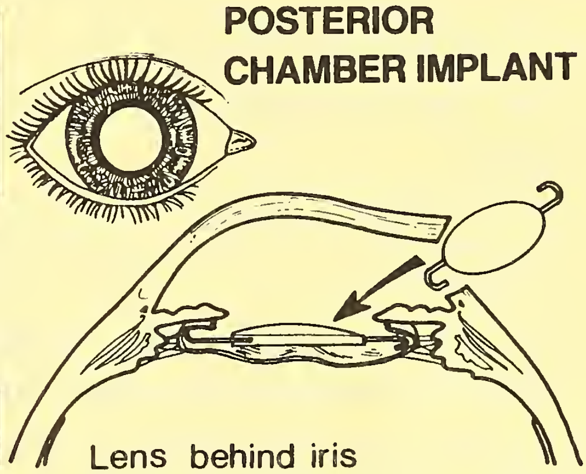


Fig. 11

22 Can I have an implant if I have glaucoma?

Yes. It is safe to put a posterior chamber implant in an eye with glaucoma. The presence of such an implant in the eye does not make the glaucoma worse.

23 Is it possible that an implant will not be put into my eye during cataract surgery even though I was told to expect one?

Yes. Although most cataract operations proceed smoothly, occasionally conditions arise during surgery that make implantation inadvisable. Your surgeon will use his best judgment at the time of surgery in determining whether an implant should be put in. Even if an implant is not put in during the cataract operation, it is possible, in some cases, to put one in at a later date.

24 Will I have pain during the operation?

No. Due to medications that make you slightly drowsy and an anesthetic solution injected around the eye, cataract surgery is a painless and comfortable procedure.

25 Will I need to use my glaucoma medications after cataract surgery?

Yes.

26 Is the implant put into my eye at the same time that my cataract is removed?

Yes.

27 During the operation, will I be able to see with the eye being operated on?

No. The anesthetic solution which is injected around the eye just before cataract surgery prevents the optic nerve (the nerve which carries visual messages) from functioning for a few hours. So during surgery, you don't see any light, the surgeon's hands, or the surgical instruments with the eye that is being operated on. Your other eye will be able to see as usual, but will be covered with sterile drapes to avoid infection in the operated eye.

28 Will both of my eyes be operated on at the same time?

No. It is best to do one eye at a time, so that you always have the use of one of your eyes while the other one heals. The second eye can be operated on a few months later.

29 Do I need to stop aspirin, coumadin, or other blood-thinners before surgery?

Yes. Aspirin and other blood-thinners prevent your blood from clotting and can produce excessive bleeding during your operation. So it is important that you tell your surgeon that you are taking these medicines. Most likely, he will have you stop it several days before surgery. You should also inform your internist about this. After surgery, you may start taking them again.

30 Should I continue other medicines until the date of surgery?

Yes. Medicines that you may be taking for conditions such as high blood pressure should be continued until the date of surgery. It is important to tell your surgeon or

ULTRASOUND SCANNER

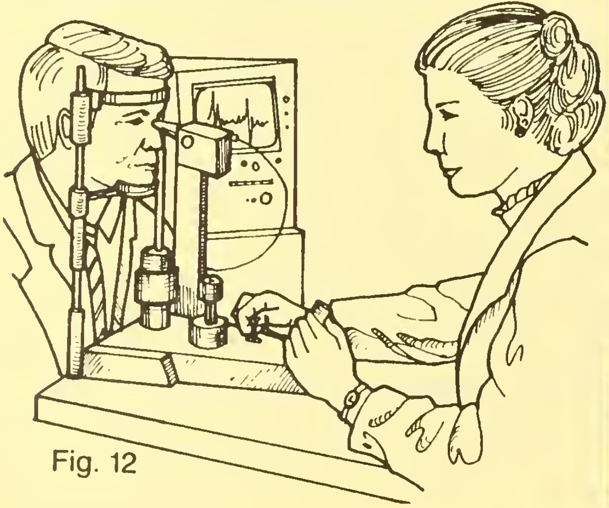


Fig. 12

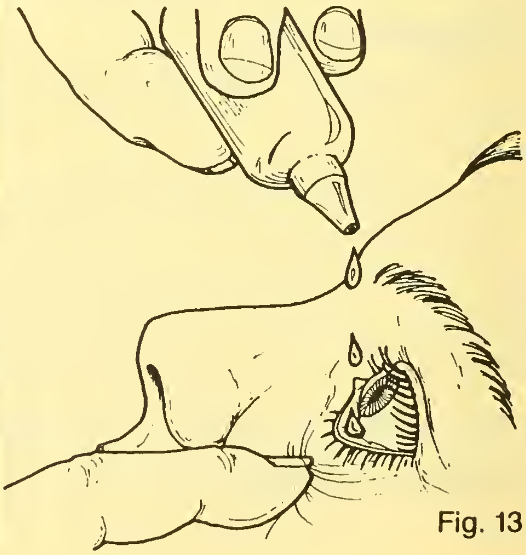


Fig. 13

his or her nurse all the medications you are using so that you can be advised appropriately.

31 What happens immediately before cataract surgery?

Before surgery, certain routine blood and urine tests, a chest x-ray, and an electrocardiogram are done. These help to ensure that all will go well for you during and after surgery.

It is important to remember not to eat or drink anything after midnight on the day before surgery. On the morning of surgery, dilating eye drops and antibiotic eye drops will be given to the eye being operated on.

After you are taken to the operating room, an intravenous (I.V.) tube is connected to your arm. Through this tube a sedative is given. This will make you quite drowsy. During this period, an anesthetic solution is injected around the eye.

After a few minutes, the skin of the eyelids, forehead and cheek on the side of the eye to be operated and the eye itself are numb. The skin is then washed with soap, water, and alcohol to make it sterile and help prevent the eye from being infected during surgery. Sterile cloth drapes are then placed over your entire head (except for the eye to be operated on) and body to further minimize the chances of an infection occurring. There is no reason to feel suffocated under the drapes because a tube bringing fresh air or oxygen will be right next to you under the drapes.

Because of the delicate nature of the operation and the tiny area being operated on, your surgeon will use a microscope to do your surgery. The microscope magnifies and illuminates the tiny operating area in your eye. After the microscope is placed in position, your surgeon is ready to start the procedure.

32 Who will be in the operating room with me?

Your surgeon, the surgeon's assistant, and a nurse who takes care of the instruments. Other nurses will also be in the operating room to help with the various details of your surgery, and an anesthesiologist will be there in case more medication is needed.

33 How will I feel and what should I do during the operation?

You will feel comfortable during surgery. You may be awake or slightly drowsy and might hear some unfamiliar sounds. If there is something that you find uncomfortable, you will be able to tell your surgeon about it through the drapes over your head. He will then correct the problem. Your greatest contribution to the success of the surgery will be to hold still and remain quiet. If you need to sneeze or cough tell your surgeon before doing so.

34 How long will the surgery take?

This varies but usually takes from 45 minutes to an hour.

35 What type of anesthesia is best for me?

Basically, there are two types of anesthesia used for eye surgery. Your surgeon will decide which is best for you.

1 **General Anesthesia:**
In this type of anesthesia a sedative is injected into the intravenous tube connected to your arm. This will make you lose consciousness completely. While you are asleep, a tube is passed through your mouth into the trachea or windpipe, the passageway leading to the lungs. One end of this tube is connected to a machine from which a mixture of anesthetic gas and oxygen is pumped into your lungs by the anesthesiologist. Long operations such as retinal surgery are best done with general anesthesia. Also, since children find it difficult to hold still during surgery, general anesthesia is best for them. A disadvantage with general anesthesia is that it usually takes you several hours to become awake and alert after surgery. In addition, you may have a mild sore throat and perhaps nausea and vomiting. With this type of anesthesia, you will know nothing about what took place during surgery. However, given the discomfort, general anesthesia may not be a great advantage.

2 **Local Anesthesia:**
In this type of anesthesia, a sedative is injected through the intravenous tube connected to your arm. This will only make you drowsy. An anesthetic solution is then injected around your eye. The needle of the syringe containing the anesthetic may hurt a little but most patients don't find it painful because they are quite drowsy when the injection is being given. When local anesthesia is given, only the eye to be operated on and that side of the face is numb. During the operation, you will be a little drowsy but awake and calm and will feel no pain. Almost all types of eye surgery are done using local anesthesia. An advantage with local anesthesia is that right after surgery, you can sit up, eat, drink or take a walk. In addition, there is no nausea and vomiting. Most eye surgeons prefer to do cataract surgery using local anesthesia.

36 How will I feel immediately after surgery?

You may be a little drowsy and may not remember much about the operation or you may be quite awake and alert. This partially depends on the type of medication that was used to make you drowsy before the operation. After surgery, most patients are surprised at how easy the whole experience was.

37 What can I do immediately after surgery?

You may eat and drink, sit up in a chair, and also walk and go to the bathroom with assistance.

38 What will my eye look like right after surgery?

Your eyelids may be a little swollen, slightly droopy and a little discolored. In a few days, the lids will appear completely normal. The eye itself may be a little red for about a week or two. This redness will also clear completely.

39 Will cataract surgery in any way change the appearance of my eye?

After the eye heals, your friends and family, looking at your eye, will probably not be able to detect any change in its appearance.

40 Will there be stitches in my eye after surgery?

Yes. Regardless of the technique used to remove a cataract, the opening made by your surgeon to provide access into the eye is closed with stitches.

41 Will the stitches have to come out?

No. The stitches are made of a special material that does not require removal. Occasionally after your eye has healed, a stitch may become loose and produce a slight irritation of the eye. It can then be easily and painlessly removed in your doctor's office. Sometimes, a few weeks after surgery, your surgeon may cut some stitches to give the eye a better shape. This, too, is completely painless and is done in your doctor's office.

42 How long will it take my eye to heal?

About six weeks.

43 Will my vision be perfectly clear immediately after surgery?

No. In fact, your vision is usually cloudy for a few days to a few weeks after surgery. The reasons for this include inflammation within the eye caused by the surgery and the gradual healing of the opening in the eye which was made to remove the cataract.

44 How soon after surgery may I use the operated eye?

Right away. You may not be able to see clearly with the eye, but there is no harm in using it, for example, to read or watch television.

45 Will I need to use eyedrops after surgery?

Yes. Eyedrops which help reduce inflammation and prevent infection are used for about six weeks after surgery (see Figure 13).

46 Will I have to wear eyeglasses after surgery?

Even though an implant has been placed in the eye, eyeglasses are usually needed to help refine your vision and make it clear. The eyeglasses you may need will have thin lenses and will not be like the thick "coke bottle" glasses which people used to wear years ago when implants were not used. If you wear eyeglasses now, you will probably need to change the lens over the operated eye a few weeks after surgery.

47 What are some conditions that may exist in my eye before surgery which may prevent good vision afterwards although perfect cataract surgery is done?

Even after perfect cataract surgery, the eye is left with problems that were present before surgery.

Glaucoma is a condition where the pressure in the eye is higher than normal. If you have a cataract and glaucoma and have lost vision from both, removing the cataract will only restore the vision you lost due to the cataract. The vision lost from glaucoma is permanent and will not be restored by cataract surgery.

Macular degenertion is an aging change in the retina which causes you to lose clear vision in the central part of your visual field. If you have severe macular degeneration and cataract, the improvement of vision after surgery may be minimal.

Diabetes can affect your retina and produce poor central vision if it affects the macula. Removal of a cataract will not eliminate this poor vision although the part of vision lost due to the cataract will be restored.

48 What are some of the possible complications of cataract surgery even though perfect surgery is done?

Infection is a serious complication which can significantly reduce vision after surgery. To help prevent this possibility, an antibiotic will be prescribed by your surgeon. Fortunately, such infections are very rare, occurring once in a thousand cases.

Hemorrhage or bleeding is a complication that ranges from mild to very serious. The worst type is called an expulsive hemorrhage and can leave the eye without vision. Fortunately, it is extremely rare and the chances of it occurring are less than one in five thousand.

A retinal detachment is a complication that occurs in 1 to 2% of people who have cataract surgery. If you are very nearsighted or myopic, you have a 4 to 5% chance of developing a retinal detachment after surgery. If you have had a previous retinal detachment which has been surgically reattached, there is an increased chance of the retina redetaching after cataract surgery. However, if the detachment is detected early, it can be reattached surgically with little loss in vision. It is important to remember that in some people, even if cataract surgery is not done, the retina can detach.

Macular edema or swelling of the macula with fluid can occur in about 20% of people who have cataract surgery. Fortunately, in almost all cases the fluid is absorbed by the eye and good vision returns. However, the time taken for this to happen is variable and may take from a few weeks to a year.

Glaucoma may occur after cataract surgery, but can be usually controlled with medicines.

49 What will my eye feel like during the first few days after surgery?

It is normal for you to feel that you have a small cinder in the eye for a few days to a few weeks after surgery. As the tissues of the eye heal, this foreign body sensation will get less and less and finally disappear.

It is important to realize that the symptoms mentioned above may vary in degree. If the foreign body sensation or tearing is very mild, there is no reason to be concerned. However, if they are severe, you should bring it to the attention of your surgeon.

50 Do I have to keep my eye covered after surgery?

Yes. Immediately following surgery, a soft eye pad made of cotton and a firm metal eye shield are placed over the operated eye and secured with adhesive tape which sticks to the skin of the forehead and cheek (see Figure 14).

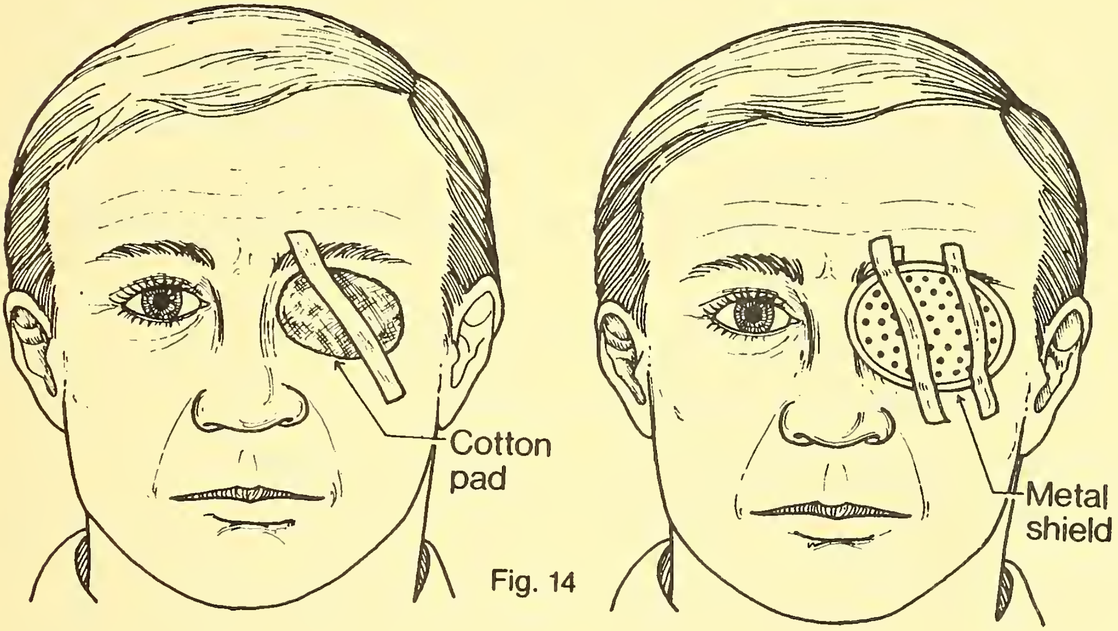


Fig. 14

On the day following surgery, you may omit the soft eye pad and use only the metal eye shield. With the operated eye, you can then look through the holes in the shield. If the eye feels more comfortable with the lids closed, you can continue to use the eye pad in addition to the metal shield.

If you wear eyeglasses, you could omit the metal shield whenever you have your glasses on. However, when the glasses are taken off for any reason, the metal shield should be put back on at once. In other words, you should always have either your glasses on or the metal shield covering the eye at all times for about 6 weeks after surgery because it takes that long for the eye to heal completely.

The important point is that there should be something firm in front of your eye to provide protection against anything that might accidentally hit or push on it. You should remember that when you go to sleep at night or if you lie down to take an afternoon nap, the metal shield must be on the eye. You should also try to sleep either flat on your back or on the side of the unoperated eye to avoid pressing on the operated eye with your pillow. Having the metal shield on the operated eye will prevent damage to the eye even if you accidentally turn to the other side during sleep. These restrictions only apply for the first six weeks after surgery.

51 How often will I have to see my surgeon after the operation?

This varies slightly between patients, but generally, you will be examined three or four times during the first two months after your operation.

52 What about physical activity after surgery?

Due to advances in surgical technique, your physical activity after cataract surgery is not as restricted as it was in the past. There is no restriction on light activities such as walking. You should avoid lifting heavy objects, bending over so that your head is below the level of your waist, jogging or doing other vigorous physical exercise for about 6 weeks after surgery. You may pick up objects from the floor but kneel when doing so instead of bending over.

53 Can I rub or press my eye after cataract surgery?

No, not for at least six weeks.

54 Can I drink alcohol after surgery?

Yes. Alcohol in moderation is permitted after surgery.

55 When can I shower and wash my hair?

You may take a shower from the neck down right after surgery. It is important that soap and shampoo do not contact the operated eye for six weeks. This will help avoid irritation and infection of the eye. During this time, a family member, a friend, or your hair dresser can wash your hair while you are lying back, but you should wear your metal shield over the operated eye. Six weeks after surgery, you may take showers as you did before surgery.

56 When can I resume driving?

Since the vision in the unoperated eye varies from one patient to another, it is best to ask your surgeon what is appropriate for you.

57 When can I go back to work?

This depends on the type of work you do. If you have a desk job, you may return to work in about a week or two after surgery. If you have a job that involves lifting heavy objects, you should wait at least six weeks.

58 How much will the surgery cost?

The cost of cataract surgery varies from one part of the country to another and also between surgeons. Most insurance plans cover a portion of the cost. Ask your surgeon or his billing clerk what the fees are.

A Note from the Editor:

Doctors do talk to their patients. We have asked doctors in North Carolina to provide us with doctor-patient talk for our Features for Patients. Our first response came not from North Carolina, but from Massachusetts. Dr. Thomas has Tar Heel roots, however; he was raised in Charlotte, and he graduated from UNC medical school in 1973.

PHYSICIANS' FORUM

Paying Physicians

Eugene W. Linfors, M.D., editor

- *The question for December is: Plumbers and electricians are paid by the hour in a perfectly acceptable fashion. Should physicians be paid for their time in the same way? How should this be controlled?*

From Dr. James H. Black, an internist from Charlotte.

Physicians' compensation cannot easily be compared to the services of electricians, et al. There are many levels of occupational skill in our country. Society has demanded that the training of a physician must produce one of the top skill levels of the many professions. Numerous attempts have been made to compute the physician's charges into an hourly schedule. The final fee charged represents the culmination of many years of competitive education and training and reflects the complexity of the specific medical problem that has been treated. An hourly fee would not justify the varying amounts of both cognitive and technical skill required to evaluate and treat the wide variety of problems facing today's physician.

I believe in the fee-for-service system which must be combined with unrestrained patterns of competition and a genuine interest in cost effectiveness. This system has played a major role in forging the highest quality of medical care now available in the world.

The increase in the overall cost of health care has been directly related to the rapid advancement of scientific technology and the resulting complex instruments that significantly improve the physician's ability to diagnose and treat.

Patients should be prepared to pay a reasonable fee for this quality of medical care. The physician's responsibility is to maintain this level of care and to let his fees reflect the principles of fairness and honesty.

From Dr. Malcolm Fleishman, an internist from Fayetteville.

Physicians should not be paid for their time in the same way as plumbers and electricians. Patients react differently to the same diseases and so do their families. The degree of difficulty and time spent thinking about the patient when not in his or her physicial presence is always a factor. Charges should be based on time and degree of difficulty. The concept of usual and customary fees to determine what charges most physicians set for cognitive skills and specific procedures is a useful one. If fees are considerably above the usual and customary, then the patient should have recourse to mediation committees of hospital staffs or medical societies to arbitrate differences.

From Dr. E. Rodney Hornbake, an internist from New Bern.

In fact plumbers and electricians are *not* paid by the hour. It is true that certain skilled laborers earn an hourly wage, but the people who are most analogous to physicians do not. Those who resemble physicians in their work are the electrical and plumbing contractors.

Consider the similarities. The contractor must hire and train those who work for him. He must accept responsibility for their work. He must bill for their services and be certain that they are paid. The contractor is licensed by the state after passing a certifying examination. A contractor whose failure to adequately perform results in injury to others may be sued for damages with subsequent harm to his reputation.

What determines the earnings of the electrical or plumbing contractor? The answer is that market forces control his earnings. The people who have cash to pay and bid for his services in the market place will determine the value placed upon his services. These are precisely the forces that determined what physicians earned before the equation was complicated by the addition of prepayment variables early in this century. The physicians who enjoyed the best reputations were in greatest demand and commanded the highest fees.

The shortcoming of this system is obvious — those without cash tend not to receive the care that they need. However, the great strengths of this system should not be overlooked. I propose that all prepayment schemes be made illegal. Only true insurance against catastrophic expenses should be allowed. Catastrophic might be defined as expenses over ten percent of one's annual income. This catastrophic insurance coverage would have to be universal and mandatory in the same way liability insurance is mandatory for drivers.

Under this system total costs would undoubtedly drop, the federal government's solvency would become more likely and we would all be rid of the nitwits trying to plan our destinies. Most importantly all of us, physicians and consumers alike, would regain something very precious — our freedom.

From Dr. Jerome Ruskin, a cardiologist from Greensboro.

Because of the ever increasing percentage of the Gross National Product devoted to health care, compensation for physicians' services has been subjected to much critical analysis in the last decade. One factor cited in a Health Care Financing Agency (HCFA) study has been the growth in real services per visit or per day (intensity). Increased intensity of services, due in part to better access to quality medical care, but primarily a function of technology-intensive diagnostic services, is seen as a major contributor to the rise in health care costs. Spurred on by the massive federal budget deficit, Congress and the Administration have already implemented cost cutting measures, including DRGs and the physician's fee freeze. Industry and such insurance programs as HMOs and PPOs have attempted to limit health care costs by other means.

One of the criticisms of the current methodology of payment for physicians' services, based on UCRs, is that it rewards physicians who order (and who may perform) high technology procedures while penalizing those who practice high quality but conservative medicine.

It is entirely feasible that a new Relative Value Scale (RVS) may be developed upon which physician reimbursement will be based. The American Society of Internal Medicine has advocated a change from the charge-based system, which is a reflection of present physicians' charges, to a "resource cost" approach. Factors to be considered include the time spent by a physician in performing a procedure or in an office visit, the complexity of the service rendered (the intensity of the physical and mental effort involved, including the risk of intraoperative complications, the diagnostic skills and clinical judgments required to choose appropriate procedures, and the technical skills required to perform the procedure), the physician's investment in professional training and the overhead expenses of physicians' practices. (Hsiao and Stason, paraphrased from the ASIM "white paper" on an alternative RVS based on resource costs.)

In response, then, to the question, my answer is "Yes, partly." I believe a resource cost-based RVS for physicians' services, of which time is but one factor, will help reward the conservative, cost conscious but effective physician, and will not interfere with the application of high technology services and procedures when indicated, while at the same time helping curb the rate of rise of the nation's health care costs. Of interest, HCFA has recently awarded a contract to Harvard University, with the AMA as a subcontractor, to construct such a cost-based RVS.

From Dr. Joseph D. Russell, an internist from Wilson.

The question of an hourly rate for physicians' services is a question which often comes up but leaves those in the medical profession with an immediate, emotional, "No, it just wouldn't work." Why wouldn't it? We assume it works well for plumbers and electricians. How can we defend a negative response to this question?

Basically plumbers and electricians figure the cost of a job based on materials, equipment, labor, overhead, and profit. Materials costs may vary according to the size of the job, specifications, and competition among manufacturers or distributors. The equipment required to complete a certain job also may affect cost, especially if amortized over a period of time, the number of uses, and depreciation.

Labor for a given job may also vary according to the availability of trained electricians or plumbers in the area or community. These rates might also vary according to the time of day, i.e., weekends, holidays, etc., and the number and type of personnel required on a particular job and their respective wages.

Overhead is a fixed cost which may vary according to fixed operating and support services and the volume of services provided by the business, and its physical plant requirements.

Finally profit is calculated based on an acceptable scale for the industry and competition within the marketplace.

Since physicians traditionally have existed as owners of their business rather than employees, all of the above factors would need to be addressed in order to come up with an acceptable hourly rate. Using current cost estimates for materials, equipment, overhead, labor, and profit, we would assume that an hourly rate could be calculated for physicians' services which would be defensible. Guarantees of outcome would be difficult to project and would then create the additional problem of how long services would be maintained, especially in cases of chronic disease, variable responses to therapy, and frequency of follow-up for maintenance or surveillance of therapy or disease.

The initiation of an hourly rate for reimbursement would likely lead to collective bargaining and possible unionization within the medical profession. The potential consequences of such actions would no doubt have extreme negative effects on the doctor-patient relationship not to mention the overall well-being of this nation and its citizens. Controls would most likely fall under the jurisdiction of the Federal Trade Commission and/or the Fair Labor Standards Act. Questions regarding antitrust as well as overtime compensation would be matched by problems concerning continuity of care and payment for cognitive services.

So, I feel reimbursement of physicians by the hour is opening Pandora's box and would use the above arguments to defend the answer, "No, it just wouldn't work."

From Dr. Phillip A. Sellers, an internist from Hendersonville.

Two basic issues related to physician reimbursement are raised by this question. (1) Should reimbursement be based solely on time spent and (2) Should physicians be organized as labor unions to obtain the advantages of unionization?

Time alone is inadequate to describe physicians' services. Rigid application of time-based guidelines for reimbursement should be opposed. However, time should be a large and important element of any reimbursement system. Several other factors — such as complexity, overhead, training of physician and risk — all need to be considered in reimbursement formulas.

Though physician income is dropping and reimbursement for physicians' services by third parties — both governmental and corporate — is decreasing, the medical profession at present generally still has its autonomy. The physician's relationship is still primarily with the patient, not with the third-party payor. We don't need to be employees with a "John L. Lewis" leader; nor do we need to be able to strike. We do need to maintain our professional relationship with our patients; this relationship, according to recent words of Dr. James Todd of the AMA, includes concern, competence, communication, conscience — with moral responsibility — and compassion.

There is no question that physician reimbursement systems are going to change more in the next one to two years than they have in the last 20-30 years, when "usual, customary and reasonable (UCR)" insurance reimbursement systems were put in place. There is no question that there is a need for change. For example, the Medicare physician reimbursement system is far too complex and complicated. It is an administrative nightmare and over the years has built up many unfair inequities for the physicians as well as for patients.

A new system of reimbursement needs to be developed. The basic ingredients should include an indemnity fee schedule based on a relative value scale of all physician services. The physician could accept this as full payment. The other necessary feature of the system should give the physician the option to "balance bill." In other words, the physician would be able to bill more than the fee schedule allows.

No, I would not like to be paid as a union electrician is paid.

- EDITOR'S NOTE:

Once again I thank all of our respondents for their opinions. I know it is difficult to find time for something extra when you are already very busy.

If I am reading these opinions correctly, time spent on the patient's problem is only one of several important parts of the reimbursement formula. A simple hourly rate for physicians might be inflexible and certainly would change the doctor-patient relationship.

A broader but related question for a later issue of the Forum is, **Will fee for service survive the pressure from alternative health care delivery systems, e.g., HMOs, PPOs, IPAs? Should it?** I would appreciate your opinions.

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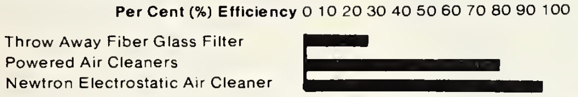

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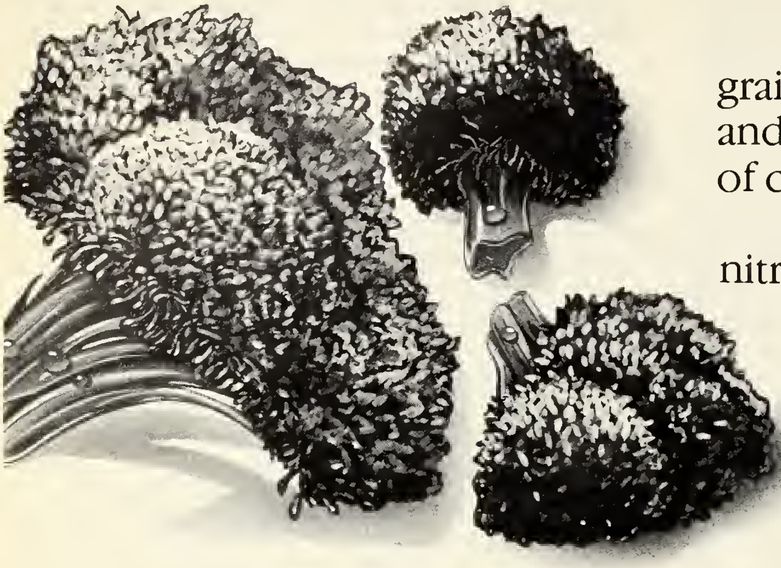

There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.

Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash and tomatoes, citrus fruits and brussels sprouts.

Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables, and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods like ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

Be moderate in consumption of alcohol also.

A good rule of thumb is cut down on fat and don't be fat. Weight reduction may lower cancer risk. Our 12-year study of nearly a million Americans uncovered high cancer risks particularly among people 40% or more overweight.

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Aspirin and Reye Syndrome: A Saga Unfolds

Floyd W. Denny, M.D.

- *While the final answer has yet to be given, prudence dictates that aspirin-containing medications be avoided in children with certain illnesses.*

REYE syndrome is a rare, acute but serious disorder of childhood in which vomiting and coma develop three or four days after a prodromal viral illness. The reported estimated annual incidence of the syndrome has varied from <1 to 6 per 100,000 children under 18 years of age.[1, 2] The death-to-case ratio has decreased in the past few years and now is almost 10% at most teaching hospitals.[3] The etiology is unknown but the prodromal viral illness usually is a respiratory tract infection, typically influenza B in children 10 to 14 years old; in children aged 5 to 9 varicella is more common; and in younger age groups the antecedent illness may be diarrhea. The Reye syndrome is manifested clinically as an encephalopathy and chemically as hepatopathology.

A number of studies have implicated salicylates as a causal factor in the Reye syndrome. Four case-control studies published between 1980 and 1982 from Arizona, Ohio and Michigan have suggested that there is an association between the ingestion of aspirin during the prodromal illness and the subsequent development of Reye syndrome.[4-8] Herein begins a saga that is continuing to unfold.

In 1980 the Centers for Disease Control (CDC) conducted a review of the reported studies and published a summary of them; CDC advised parents to use caution when administering salicylates to children with viral illnesses, particularly chicken pox and influenza-like illnesses.[6] In 1981, the National Institutes of Health held a consensus development conference on the diagnosis and treatment of Reye syndrome; the consensus panel recommended prudence in the administration of salicylates to children with influenza and varicella.[9] Also in 1981 the CDC convened a working group of consultants, including representatives from the American Academy of Pediatrics and its Committee on Infectious Diseases and Drugs to review the relationship between Reye syndrome and salicylates that had been reported in the four case-control studies. These consultants concluded "that it was unlikely for the limitations of the studies, either singly or in combination, to explain totally the strength and consistency of the observed association between Reye syndrome and salicylates."[6] There then followed meetings between representatives from the CDC, the Food and Drug Administration and drug manufacturers which resulted in 1982 in the issuance of a Surgeon General's Advisory on the Use of Salicylates and Reye syndrome, which was published in the Morbidity and Mortality Weekly Report.[10] The Advisory concluded: "As a result of this entire review process, the Surgeon General advises against the use of salicylates and salicylate containing medications for children with influenza and chickenpox." The same month that this was published the American Academy of Pediatrics Committee on Infectious Diseases and Drugs published a statement advising that the use of salicylates should be avoided for children suffering from influenza or chickenpox.[11] With this impetus, the FDA began the process to change labeling of salicylate-containing products and issued by the end of the year an advance notice of proposed rule making.[12]

There then followed considerable disagreement among federal agencies, pediatricians and aspirin manufacturers about the weight of evidence in the four case-control studies. For example, in November 1982, the Executive Committee of the American Academy of Pediatrics issued a statement that "Labeling should be delayed until more conclusive evidence of the association of aspirin administration and the Reye syndrome is shown by further investigation."[13] Until this day there are no warning labels on aspirin containers. This widespread hassle and uncertainty was so great that the Secretary of the Department of Health and Human Services appointed a Public Health Service Task Force comprised of members of the National Institutes of Health, Food and Drug Administration, and CDC to design and implement a new epidemiologic study concerning the nature of the possible relationship between Reye syndrome and medications.

A pilot study was conducted between February and May 1984 to determine the study feasibility and to establish methodology. Although this was a pilot study and definitive answers were not anticipated, the results were so astonishing that they were quickly called to medical attention in the Morbidity and Mortality Weekly Report.[14] The study included 29 Reye syndrome cases and four control groups containing a total of 143 children. Ninety-seven percent of the case children were reported to have received salicylates during a respiratory or chickenpox illness before a clinical-

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From the Program for Health Promotion and Disease Prevention, UNC School of Medicine, Chapel Hill 27514.

ly defined onset of Reye syndrome compared with 28-59% of the control groups at any time during their matched illnesses. The risk defined in this pilot study was comparable to or greater than that determined in the previously reported studies. Following a review of these data, an Institute of Medicine/National Academy of Sciences Review Committee recommended:

1. The PHS Task Force should proceed with the full study.
2. Results of the pilot study should be released promptly to the public and to scientists for review and analysis.
3. Analysis of the pilot study data reveals a strong association between the Reye syndrome and the use of aspirin; considering data from previous studies also show an association of use of aspirin and Reye syndrome, the Committee recommends that steps should be taken to protect the public health before the full study is completed.
4. Although it is impossible to know with certainty whether the release of the pilot study data will harm the full study, the Committee suspects the effects of the attendant publicity will be no more damaging than the current climate of public opinion, which appears not to have impeded conduct of the pilot study.

In concluding its presentation in the Morbidity and Mortality Weekly Report, the editors state, "A report of the pilot study is currently being prepared for publication. In view of these preliminary findings, physicians, parents, or older children who self-medicate should continue to be advised of the probable increased risk of Reye syndrome associated with the use of salicylates for children, including teenagers, with influenza-like illness or chickenpox."

Thus, the saga of the association between aspirin and Reye syndrome continues and may be far from over. Great controversy rages over the adequacy of all of the epidemiological studies reported up to this time. The interested reader is advised to observe carefully future publications and news releases that might clarify this issue. It is of interest to note that fewer cases of Reye syndrome were reported in 1985 than in recent years (CDC, personal communication); the number of cases occurring now may preclude further epidemiological studies. The cause for this is unknown. Until a final answer is obtained it would seem prudent for physicians, parents and children alike to be cautious in the use of aspirin in varicella and viral infections of the respiratory and gastrointestinal tracts.

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Confused About Advertising?

Thomas V. Bennett

- *Advertising by doctors is increasing. The* North Carolina Medical Journal *can reject or accept advertising as it wishes. The North Carolina Medical Society cannot prevent ads from being placed in any of the public media — newspapers, magazines, radio, television. This subject has recently been covered in the* Bulletin *of the North Carolina Medical Society. It is being republished in the* Journal *because many persons missed it. The Editor believes that the first rule of teaching is repetition.*

PHYSICIAN advertising used to consist of a name on a sign and a listing in the telephone directory. Physicians built their practices through referrals from colleagues or word-of-mouth "advertising" by patients. It was considered unprofessional and unethical to do more.

But things have changed.

In the words of the North Carolina Medical Society's legal counsel, Julian D. Bobbitt, Jr., "The Federal Trade Commission continues to take an aggressive position regarding any limitations on professional advertising." The American Medical Association is operating under an FTC injunction that limits the restrictions that a professional group can place on advertising.

Some physicians want to advertise; others strongly disapprove of it. To clear the air and ease the controversy, the NCMS House of Delegates has directed that the Society report to members on the laws that define the limits of physician advertising.

The current status of the law is reflected in section 5.01 of the 1984 edition of *Current Opinions of the Judicial Council of the American Medical Association*. An AMA spokesman summarized the section by saying, "Essentially, a physician can advertise as much as he wants, as often as he wants, through any medium he wants, as long as he isn't deceptive or misleading."

Section 5.01 offers some noteworthy specifics:

"There are no restrictions on advertising by physicians except those that can be specifically justified to protect the public from deceptive practices. A physician may publicize himself as a physician through any commercial publicity or other form of public communication (including any newspaper, magazine, telephone directory, radio, television or other advertising) provided that the communication shall not be misleading because of the omission of necessary material information, shall not contain any false or misleading statement, or shall not otherwise operate to deceive.

"The form of communication should be designed to communicate the information contained therein to the public in a direct, dignified and readily comprehensible manner. Aggressive, high pressure advertising and publicity may create unjustified medical expectations. Any advertisement or publicity, regardless of format or content should be true and not misleading.

"The communication may include: (a) the educational background of the physician; (b) the basis on which fees are determined (including charges for specific services); (c) available credit or other methods of payment; and (d) other information about the physician which a reasonable person might regard as relevant in determining whether to seek the physician's services.

"Testimonials of patients, however, as to the physician's skill or the quality of his professional services should not be publicized. Statements relating to the quality of medical services are extremely difficult, if not impossible, to verify or measure by objective standards. Claims regarding experience, competence and the quality of the physician's services may be made if they can be factually supported and if they do not imply that he has an exclusive and unique skill or remedy. A statement that a physician has cured or successfully treated a large number of cases involving a particular serious ailment may imply a certainty of result and create unjustified and misleading expectations in prospective patients.

"Consistent with Federal regulatory standards which apply to commercial advertising, a physician who is considering the placement of an advertisement or publicity release, whether in print, radio or television, should determine in advance that his communication or message is explicitly and implicitly truthful and not misleading. These standards require the advertiser to have a reasonable basis for claims before they are used in advertising. The reasonable basis must be established by those facts known to the advertiser, and those which a reasonable, prudent advertiser should have discovered.

"As used herein, references to a 'physician' apply also to information relating to the physician's group, partners or associates. Any communication or message within the scope of this opinion should include the name of at least one physician responsible for its content.

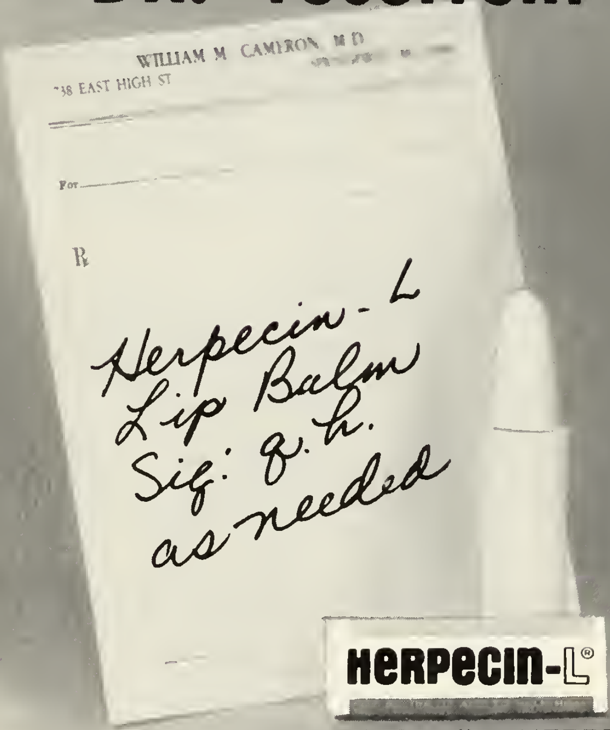
"Nothing in any opinion of the Judicial Council is in-

Reprinted from the *Bulletin* of the North Carolina Medical Society, November 1984.

tended or shall be construed to discourage or to limit advertising and representations which are not false or deceptive within the meaning of Section 5 of the Federal Trade Commission Act."

The law is permissive. It opens the door for professional advertising, and Mr. Bobbitt noted that attempts to limit a physician's advertising create a legal risk.

Dx: recurrent herpes labialis



"HERPECIN-L is my **treatment of choice** for perioral herpes." GP, NY

"HERPECIN-L appears to actually **prevent** the blisters . . . used **soon enough.**" DDS, MN

"HERPECIN-L®. . . a **conservative approach** with **low risk/high benefits.**" MD, FL

"Used at **prodromal symptoms** . . . blisters **never formed** . . . remarkable." DH, MA

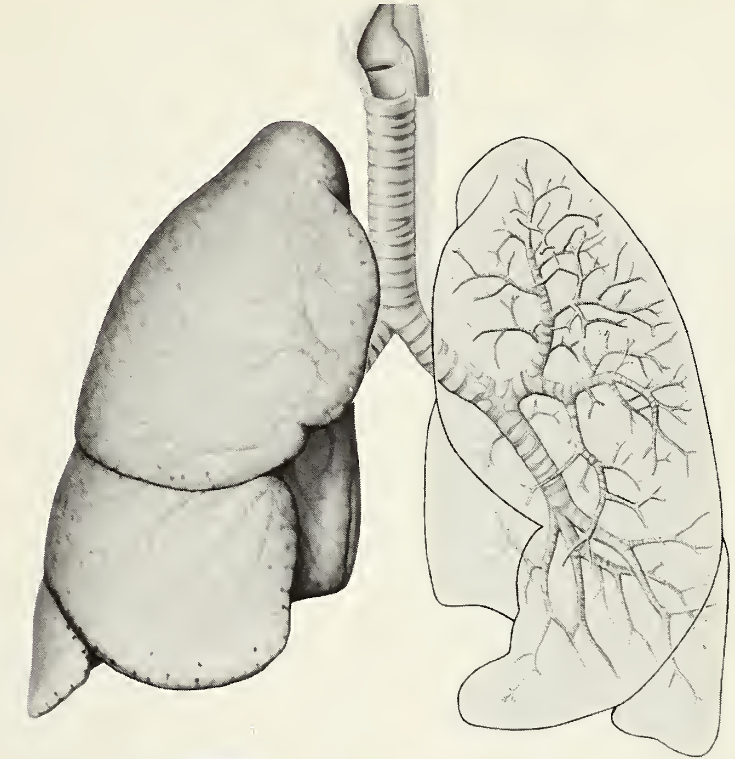
"(In clinical trials) . . . **response** was **dramatic. HERPECIN-L** . . proven **far superior.**" DDS, PA

"All patients claimed **shorter duration** . . . at **prodromal symptoms** . . . HERPECIN-L **averted** the attacks." MD, AK

OTC. *See P.D.R.* for information. For samples to make your own clinical evaluation, write: CAMPBELL LABORATORIES, INC., P.O. BOX 812-MD, FDR STATION, NEW YORK, N.Y. 10150

In North Carolina HERPECIN-L is available at all *Crown, Eckerd, Kerr, Mutual Drug, Revco Drug Stores* and other select pharmacies.

Consider the causative organisms...



Ceclor®
cefaclor

250-mg Pulvules® t.i.d.

offers effectiveness against the major causes of bacterial bronchitis

H. influenzae*, *H. influenzae*, *S. pneumoniae*, *S. pyogenes
(ampicillin-susceptible) (ampicillin-resistant)

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions* – If an allergic reaction to Ceclor® (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy – Pregnancy Category B – Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor® (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers – Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children – Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbiliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain – Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic – Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic – Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal – Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note. Ceclor® (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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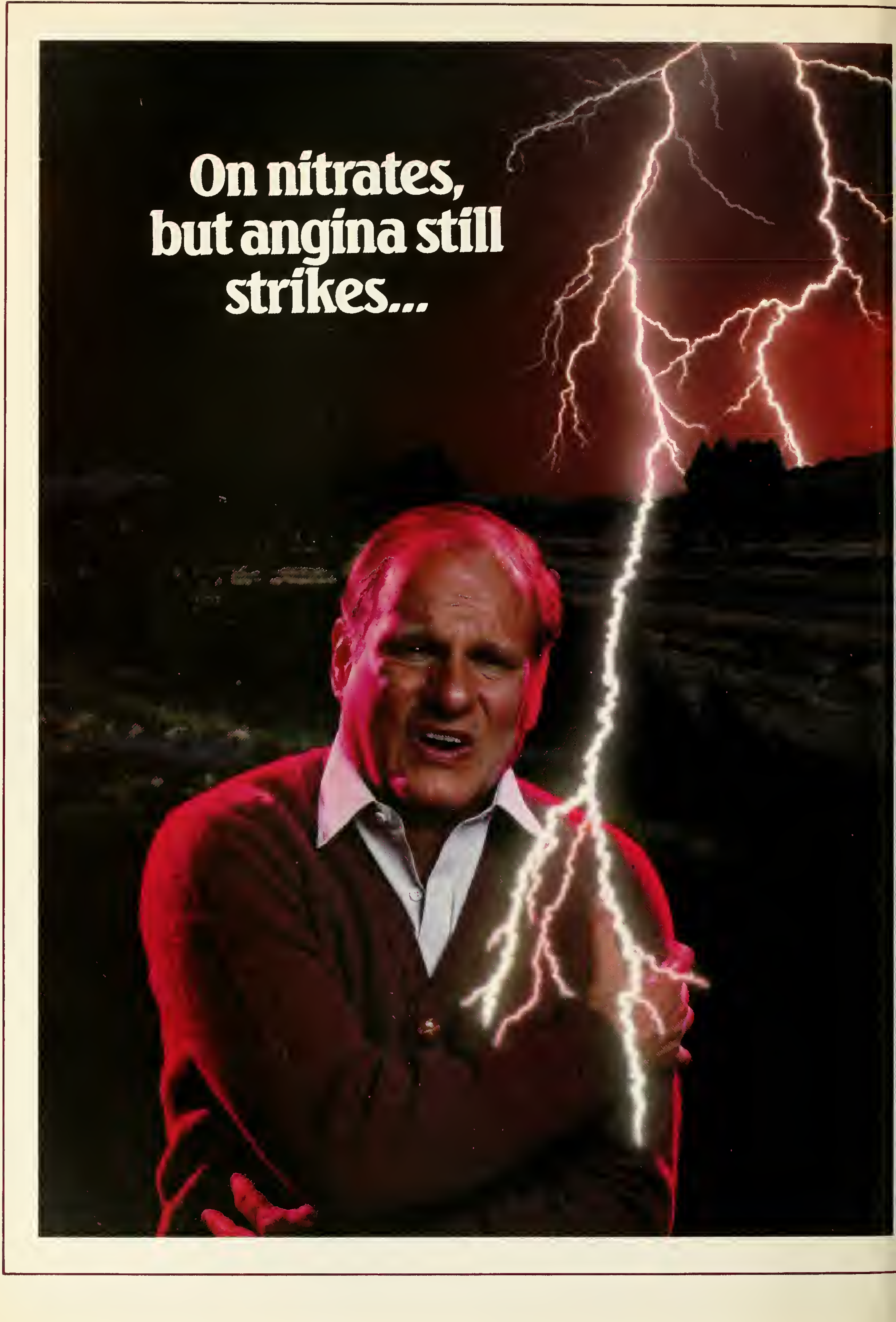
On nitrates, but angina still strikes...

After a nitrate, add ISOPTIN®

(verapamil HCl/Knoll)

To protect your patients, as well as their quality of life, add Isoptin instead of a beta blocker.

First, Isoptin not only reduces myocardial oxygen demand by reducing peripheral resistance, but also increases coronary perfusion by preventing coronary vasospasm and dilating coronary arteries — both normal and stenotic. These are antianginal actions that no beta blocker can provide.

Second, Isoptin spares patients the beta-blocker side effects that may compromise the quality of life.

With Isoptin, fatigue, bradycardia and mental depression are rare. Unlike beta blockers, Isoptin can safely be given to patients with asthma, COPD, diabetes or peripheral vascular disease. Serious adverse reactions with Isoptin are rare at recommended doses; the single most common side effect is constipation (6.3%).

Cardiovascular contraindications to the use of Isoptin are similar to those of beta blockers: severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no artificial pacemaker is present) and second- or third-degree AV block.

So, the next time a nitrate is not enough, add Isoptin…for more comprehensive antianginal protection without side effects which may cramp an active life style.

ISOPTIN. Added antianginal protection without beta-blocker side effects.

Please see brief summary on following page.

ISOPTIN®

(verapamil HCl/Knoll)

80 mg and 120 mg scored, film-coated tablets

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction < 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. (See *Precautions*.) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before ISOPTIN is used. (Note interactions with digoxin under *Precautions*.) ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild and controlled by decrease in ISOPTIN dose). Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment; however, four cases of hepatocellular injury by verapamil have been proven by rechallenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN. Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported. (See *Warnings*.) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shakiness, claudication, hair loss, macules, spotty menstruation. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984. 2385

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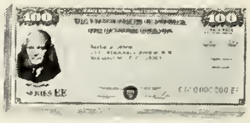

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The Silent Ectopic Pregnancy

Linda M. Frazier, M.D.

- *A "benign" abdomen does not rule out ectopic pregnancy*

ECTOPIC pregnancy is a life-threatening condition affecting approximately 52,000 women each year in the United States.[1] Only a minority of patients present with the classic textbook picture of a missed menstrual period, sudden lower abdominal pain, exquisite adnexal tenderness and shock. We recently cared for a patient whose ectopic pregnancy presented with relatively minor findings.

This 33-year-old woman had had two normal vaginal deliveries. She had a Progestasert intrauterine contraceptive device (IUD); there was no history of salpingitis, pelvic inflammatory disease or endometriosis. Menstrual periods were regular.

On the day before she was seen, her menstrual period began, on time, but she developed dull right lower quadrant pain; this type of pain was unusual for her. She had two watery bowel movements but no cramps, fever, nausea or vomiting. There was no breast pain or fatigue. She did not appear ill. Her temperature was 36.5° C; there was right lower quadrant tenderness with equivocal rebound accentuation; the IUD string was visible; there was mild tenderness on cervical manipulation; there was no adnexal mass or tenderness. Hemoglobin, which had been 14.5 g several months earlier, was 11.6 g; mean corpuscular volume was 95. White blood cell count was 6700 with 76% neutrophils, 10% lymphocytes, 7% monocytes and 1 lymphocyte variant.

A diagnosis of appendicitis was considered so the patient was asked to return for a follow-up evaluation the next day. By then her menstrual period had stopped prematurely and she felt much better. A serum human chorionic gonadotropin (hCG), beta-subunit, was ordered because of the possibilty of an ectopic pregnancy. Temperature was 37.5°C; her abdomen was only minimally tender. The serum specimen was misplaced by the laboratory but the test was not repeated because she was improving and there was no adnexal tenderness. Two days later she was feeling well. Two days after that, the serum specimen was found. The pregnancy test was positive.

When contacted later that day, the patient said she felt completely well, but that her period had begun again. That evening a pelvic ultrasound showed no evidence of intrauterine pregnancy; the oviducts could not be visualized because of a moderate amount of pelvic fluid. She consented, a little reluctantly, to hospital admission. Pelvic examination was again unremarkable. Quantitative hCG levels progressively increased to 3300 mIU/mL (figure 1). Differential diagnosis included ectopic pregnancy and abortion of an intrauterine pregnancy. Dilation and curettage were negative; laparoscopy showed a 2.5 cm right infundibular ectopic pregnancy (figure 2). A distal salpingectomy was performed. Approximately 300 cc of intraperitoneal blood was found. The patient recovered without incident.

This patient's initial right lower quadrant pain was probably caused by intraperitoneal bleeding from her ectopic pregnancy. When the bleeding stopped peritoneal inflammation improved and her pain resolved. The infundibular location of the conceptus allowed it to expand without causing as much pain as may have occurred in the narrower ampullary or isthmic oviduct.

Ectopic pregnancies present with subacute or atypical manifestations in up to 85% of cases.[2] Delay in diagnosis increases the risk of tubal rupture and death by exsanguination. In a series of women successfully treated for ectopic pregnancy, only four of 26 were correctly diagnosed on initial presentation.[3] In another series, there was an average delay of three days between the patient's first contact with a physician and hospital admission.[4] Fortunately, the maternal death rate from ectopic pregnancy has been steadily decreasing, reaching a rate of 0.9 deaths per 1000 cases in

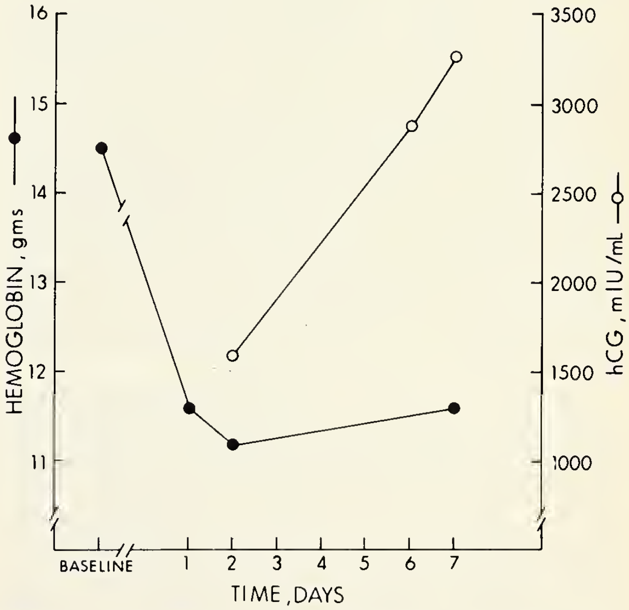

Figure 1. *Confirmation of viable trophoblastic tissue by rising human chorionic gonadotrophin (hCG) levels in this patient. Hemoglobin values fell, probably from her intrapelvic bleeding.*

From the Department of Medicine, Duke University Medical Center, Durham 27710.

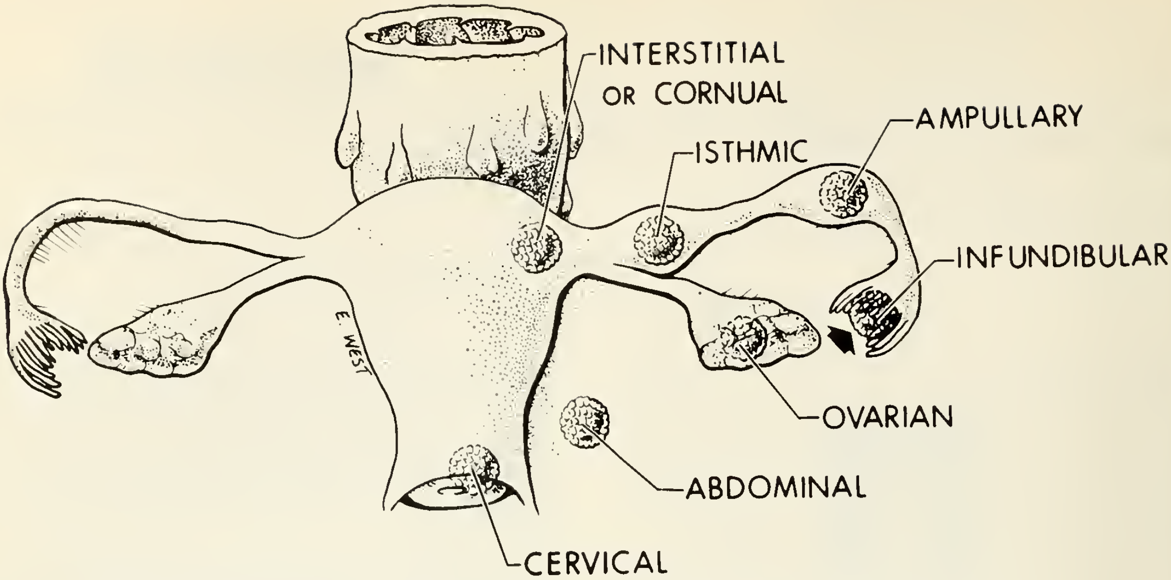

Figure 2. *Implantation sites in ectopic pregnancy. Arrow indicates pregnancy site in this patient.*

1980.[1] This decline may largely be due to earlier detection resulting from improved diagnostic techniques. Even so, one recent report estimated that 75% of maternal deaths could be prevented by prompt treatment.[4]

Ectopic pregnancies commonly present with mild or subtle symptoms so the physician must maintain a high index of suspicion. Breast soreness, nausea and other symptoms of early pregnancy may be absent. Regular menses may persist in 20-40% of patients,[2, 3] due to the inability of the abnormal embryo to stimulate the hormonal changes necessary to prevent endometrial shedding.

Abdominal pain is nearly always present in ectopic pregnancy, but the pain is unilateral in only 33%.[5] Our patient was unusual because she had minimal adnexal tenderness and because her abdominal pain resolved.

It may be difficult to differentiate between ectopic and intrauterine pregnancy. In one series, abdominal pain and amenorrhea were found in 81% of women who were found to have intrauterine pregnancies.[3]

Ectopic pregnancies have been reported in patients using every form of contraception.[6] Patients using IUDs are not at greater risk for ectopic pregnancy than patients using no form of contraception,[6] but use of an IUD does not prevent ectopic pregnancies either. Patients who have had tubal ligations or who use barrier methods have the lowest ectopic pregnancy rates. Patients using contraceptives, which prevent ovulation, have rates similar to patients using barrier methods.[6]

The cause of ectopic implantations remains poorly understood. A history of pelvic inflammatory disease is an important risk factor because tubal patency and peristalsis may be impaired. A history of pelvic infection or microscopic evidence of prior infection is present in approximately 20-40% of patients with ectopic pregnancy.[2, 6] Tubal blockage is not the only cause of ectopic implantation because the embryo is often found in the oviduct contralateral to the side where ovulation occurred.[6] Other etiologic hypotheses include delayed ovulation, retrograde menstrual flow and abnormal hormonal mechanisms.[2, 6] In approximately one third of ectopic pregnancies, the karyotype of the zygote is abnormal, suggesting that ectopic implantation may also be caused by non-maternal factors.

Ectopic pregnancy should be suspected in women of child bearing age who develop pelvic pain. The present case shows that lack of an adnexal mass or tenderness should not dissuade the physician from considering the diagnosis. Use of serum hCG testing in conjunction with pelvic ultrasonography accurately predicts ectopic pregnancy in 93% of cases.[3] The hCG may be negative if the zygote has degenerated or if the laboratory threshold for a positive hCG is too high. If this occurs, quantitative hCG tests and laparoscopy generally make the diagnosis. Some authors recommend the use of culdocentesis but this is a painful procedure which is nondiagnostic in 23% of patients with surgically-proven ectopic pregnancies.[3]

In our patient, the diagnosis of ectopic pregnancy was suspected on the basis of unilateral abdominal pain and menstrual irregularity. Her course was unusual because the pelvic tenderness resolved, but the diagnosis was confirmed by rising quantitative hCG values and laparoscopy. Subacute manifestations are common in ectopic pregnancy, so the diagnosis should be suspected on the basis of the history even when the abdominal examination is "silent."

Acknowledgment

Supported in part by a Daland Fellowship of the American Philosophical Society.

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IN STATE

December 18

New Uses of Calcium Channel Blockers
Place: Sanford
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage Street, Sanford 27330. 919/774-6518

January 10-11, 1986

Advanced Cardiac Life Support
Place: Chapel Hill
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

January 30, 1986

Controversies in Transplantation
Place: Chapel Hill
Credit: 7 hours Category I AMA
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

February 12

Affective Disorders: Diagnosis and Treatment
Place: Greenville
Credit: 3.5 hours Category I AMA
Fee: $30
Info: Office of CME, ECU, Box 7224, Greenville 27835-7224. 919/758-5200, ext. 208

February 13-14

Laser Workshop in Neurosurgery
Place: Chapel Hill
Credit: 15 hours Category I AMA
Fee: $750
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

February 14-15

House Officer Selection
Place: Chapel Hill
Credit: 12 hours Category I AMA
Fee: $335
Info: W. B. Wood, M.D., 231 MacNider 202H, UNC, Chapel Hill 27514. 919/962-2118

The North Carolina and South Carolina Societies of Pathologists Joint Winter Meeting and Annual Shelley Memorial Lecture and Diagnostic Slide Seminar will be held at the Charlotte Memorial Hospital and Medical Center, Charlotte, North Carolina, on Saturday, February 1, 1986.

The guest lecturer will be Dr. Joseph Eggleston, Professor of Pathology and Director of Surgical Pathology at the Johns Hopkins Hospital, Baltimore, Maryland.

The title of the lecture is "In Search of Small Cell Carcinoma of the Lung" and will be presented at 10:00 a.m.

Afternoon Diagnostic Slide Seminar on lung lesions 2:00-5:00 p.m. Banquet at 7:00 p.m.

For further information, call Dr. Marie-Claire Marroum at 704/338-2251.

OUT OF STATE

January 24-26

Winter Conference on Geriatrics
Place: Hot Springs, VA
Info: Mary Anna Hendley, NC Academy of Family Physicians, Box 20146, Raleigh 27619. 919/781-6467

February 1-5

Dermatology for Non-Dermatologists
Place: Acapulco, Mexico
Info: Division of Dermatology, Box 3135, DUMC, Durham 27710. 919/684-2504

February 1-8

Urologic Update
Place: Vail, CO
Credit: 25 hours Category I AMA
Info: Linda Mace, Box 3707, DUMC, Durham 27710. 919/684-8111

February 21-23

1986 Annual Meeting and Scientific Session, Virgina Chapter, AAP and The Virginia Pediatric Society
Place: Williamsburg, VA
Credit: 15 hours Category I AMA
Info: Betti Prentice, 804/643-8130

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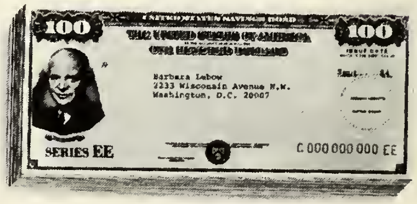

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Letters to the Editor

More Medical Words

To the Editor:

A few months ago we catalogued a collection of patients' medical malapropisms, nonstandard dialect and slang terms.[1] A number of readers subsequently forwarded to us some of the terms they have heard being used in medical settings.* Several contributors independently suggested an additional subclassification: medical transcription malapropisms, *perineal plastic syndrome* and *Highland membrane disease,* for example. Another physician proposed the topic of horrors emerging from punctuation-free nursing notes (e.g., ''Large foul green stool seen walking down the hall''). We have not, however, investigated any of these subclassifications further.

Since the preparation of our initial lexicon, James D. Thomas has written about some of the problems faced by members of the American subculture of Gypsies as they interact with the health care system and some of the particular medical terms used by them.[2] Thomas' work complements that of Snow, who focuses on the problems germane to some Black Americans in similar settings.[3] We have also read an essay by F. Gonzalez-Crussi which makes reference to several hundred colloquial terms used to describe male genitalia.[4] It is our purpose here to present the terms submitted to us along with some additional ones recently discovered by the first author. As in the previous collection of medical terms, patient medical talk is divided into the two categories of *Malapropism* and *Slang and Nonstandard Dialect*. In the former, standard medical terminology is mispronounced, becoming confused with other items of standard English vocabulary; in the latter, terms may be particular to a certain region or subculture.

Malapropisms

Article Artery
Arthuritis Arthritis
Babygel Basogel
goutch Gout
Insensitive Care Unit Intensive Care Unit
Intentional Care Intensive Care
janitor Vagina
Old Timers' Disease Alzheimer's Disease
pajamal itch Vaginal itch
penicillium Penicillin
pinwheels Pinworms
Primavera Provera
pulse Pus
subscription Prescription
sulfur Sulfonamide
TAP smear PAP smear
technical shot Tetanus shot
tenderlitis Tendonitis
tentacles Testicles
thrash Thrush
wheazels in the chest Wheezes; specifically asthmatic
whelps Welts or urticaria
wound Womb

Slang and Nonstandard Dialect

clap Urethral discharge due to gonorrhea
cold Mucus
grimes Groin
hair cut Chancre
heart dropsy Swelling of the ankles due to heart failure
hunya Hernia
kidney hurting Dysuria
knots Lymph nodes
lambooda Libido
leaders Tendons or ligaments, especially in the neck
loose bowels Diarrhea
migram headaches Migraine headaches
phlegm Upper respiratory tract infection
pocketbook Vagina
poor in blood Anemia
punish Pain (as in ''It punishes me right smart'')
sexin To have sexual intercourse with
side pleurisy Any thoracic wall pain
suage down 1. Loss of edema or swelling 2. Lose weight
sumpin' tee Anorexia (perhaps from, ''something to eat'')
tired blood Malaise
whites, the Vaginal discharge

References

1. Sugarman J, Butters RR. Understanding the patient: medical words the doctor may not know. NCMJ 1985;46:415-17.
2. Thomas JD. Gypsies and American medical care. Ann Intern Med 1985;102:842-45.
3. Snow LF. Folk medical beliefs and their implications for care of patients: a review based on studies among Black Americans. Ann Intern Med 1974;81:82-96.
4. Gonzalez-Crussi F. Notes of an anatomist. San Diego: Harcourt Brace Jovanovich Pub, 1985:110-29.

Jeremy Sugarman
Ronald R. Butters
Box 2849
Duke Hospital
Durham 27710

To the Editor:

You have probably received hundreds of these since the publication of the list of unusual words used to describe medical conditions. I had heard most of them before, but came across one yesterday that I had never heard before. You may wish to keep this in your files.

An eighty-year-old lady who had grown up down on the eastern coast was describing allergic symptoms of postnasal drip. In describing this, she said that sometimes she felt her ''Sunday tongue'' was down all the way to the bottom of her throat. We discussed this a little while longer and it was perfectly clear that what she was describing was a boggy uvula related to allergic sinusitis.

---

*Contributors were the following people: Junius W. Davis, Hester Giddings, Jared Goldstein, James L. Mathis, Bruce K. Morgan, George Olt, James G. Peden, Adrena J. Perry, Marylin Telen, John L. Weinerth, J. W. Wright, and Richard C. Zahn.

I have enjoyed the *Journal* very much over the years, and in particular the recent immense improvement in the entire operation. Keep up the good work and thank you for devoting so much of your time to this concern.

Margaret Nelsen Harker, M.D.
Morehead City 28557

It's Still Hard to Make a Living

To the Editor:

Not that long ago the *Journal*[1] was kind enough, perhaps lacking copy shortly before deadline, to publish some meditations of mine about how hard it can be for some people to make a living. Floyd Rogers, a talented reporter for the *Winston-Salem Journal*, read the article and decided that it held promise for a news story. We discussed the matter by phone and then over coffee and I deluged him with reprints about obscure occupational hazards and the like as well as telling him more about the history of occupational disease than he really needed to know.

A few Sundays later his story appeared,[2] rather less pedantic and more sprightly than becomes a medical academic but as it turned out better attuned to the vulgar ear. That very night, someone from a press service in the north called me about midnight for an interview since I now apparently qualified as a medical expert. Struggling out of sleep I sought, without sounding surly, to answer questions which he really seemed to have already answered himself.

During the next few weeks I received phone calls from friends, clippings from our Office of Information and from other friends and even a copy of an editorial from the newspaper in my wife's hometown, Shelby, accusing me ever so gently of pulling the public leg. Since some of the calls came from people I had never heard of who had suffered from Honda hip and other anatomic insults, I wrote a letter to the editor so that my wife's friends wouldn't think that I made a habit of perpetrating hoaxes. And when a Honda dealer reported that he had had customers complain of similar troubles I felt even better about the matter. My patient who suffered that syndrome in the first place recently returned for his annual physical and reported that he is still symptom-free and that he enjoyed vicarious, if anonymous, pleasure in recognizing his medical past in print. He also reminded me that it had been a Honda Accord, not a Civic, which had led to his distress.

Others called too, seeking medical advice for themselves and their friends, victims of a variety of pedestrian difficulties. A helicoptor designer even called from Fort Worth because the story had appeared in a Dallas newspaper. It seems that cockpits of helicoptors are in need of being redesigned because of technological advances and because veteran helicopter pilots get all sorts of aches and pains from sitting at the controls for long periods. Sadly I could offer no constructive suggestions although it occurred to me later that medical institutions featuring heliports might require expert personnel, or personnel which would become expert in a short time, and would be happy to publicize their efforts in the air by trotting out their authorities for him.

To my knowledge versions of the story appeared in newspapers in Asheville, Charlotte, Statesville, Rocky Mount, Salisbury, Boone, Shelby, Greenville, New Bern, Chapel Hill, Durham, Henderson, and Gastonia, NC; Columbia and Myrtle Beach, SC; Birmingham, Houston, Dallas, Richmond, Cincinnati, Reading, PA and Jonesboro, AR. So for a brief moment both the *Journal* and I had a bigger audience than usual. My transient celebrity was pleasant but I wouldn't want to make it a habit.

John H. Felts, M.D.
Bowman Gray School of Medicine
Winston-Salem 27103

References

1. Felts JH. Sometimes it's tough to make a living. NC Med J 1985;46:195.
2. Rogers F. Honda hip no fun, but chicken packer's hands is serious. Winston-Salem Journal May 5, 1985:A17.

Still Following Family Medicine

To the Editor:

I read with interest Dr. Estes' editorial "Family Medicine at Duke: A Followup" in the September 1985 issue of the *NCMJ*. I am pleased that the subsequent development of the East Carolina University School of Medicine proves Dr. Estes' chauvinistic 1973 comments wrong: "The usual answer is 'But that's not Duke's role! Let East Carolina do it.' It is a difficult job, but that should certainly be no justification for assigning that task to a school less capable than Duke."

North Carolina is fortunate to have four excellent medical schools with different attributes. East Carolina may not perform some activities such as basic science research, at the same level as Duke. However, East Carolina has filled needs that Duke and other institutions were unable to fill, in part by establishing a regional medical center in a previously underserved area. And it has done so with excellence. As an alumnus of both Duke and East Carolina, I have seen the strengths of both institutions, which are different. I am proud to have attended both schools and do not feel that my years at East Carolina were spent at "a school less capable than Duke," just at a school serving a much different purpose than Duke.

Kenneth E. Olive, M.D.
Chief Medical Resident
Wright-Patterson AFB, Ohio 45433

To the Editor:

The editorial by Dr. E. Harvey Estes, Jr., "Family Medicine at Duke: A Follow-Up," in your journal of September 85 causes me some concern. About two months ago in your journal under the classified ads, there was a solicitation for a family practice physician to join a clinic in the middle part of our state with a starting salary of $72,000 per year or 50% of the gross, whichever would be the larger. To support the proliferation of family medicine physicians on a financial basis is rather ludicrous. I have been in medicine for thirty years and in private practice for nine and one half years. I am one of three neurologists who practice together at the Durham Clinic. I do not make $72,000 a year after thirty years in practice and being in a subspecialty. Are they really going to try and tell me that starting a brand new family practitioner at $72,000 a year is the way to save society money? It has been my experience over the last nine years that family practitioners often complain about the "exorbitant fees" charged by subspecialists for consultations and then turn around and walk to the bank with a larger check each month than many of the subspecialties in this area.

As of twelve months ago — and I don't have more recent data — a return appointment to the Family Medicine Center here in Durham cost at least as much if not more than a return visit to see one of the three neurologists here in Durham. I find it difficult to consider that to be "cost effective."

I think family medicine will save society money much as the "compact cars" do today. Unfortunately medicine is much like most of our other big businesses in the United States; the attitude is one of "let the other guy save money."

A. W. Renuart, M.D.
1830 Hillandale Road
Durham 27705

The author responds:

Dr. Olive's comments are welcomed. Remember that the comment he cites was written in 1973, and was made to an audience of those who held such views. He is correct, we do have four excellent medical schools. Each *is* different. We have every reason to be proud of East Carolina, which does take its role seriously, and is particularly supportive of family medicine. I can assure Dr. Olive that I respect and admire ECU for its social responsibility to its region. It is a model for us all!

I can assure Dr. Renuart that the starting salary example he cites is a bit atypical, but it does underscore the fact that family physicians are in demand. It is also not unusual to find starting salaries in smaller communities higher than those in more crowded locations such as Durham. I cannot comment of the relative cost of visits to family physicians and neurologists, since I have no data for comparison.

E. Harvey Estes, Jr., M.D.
Division of Family Medicine
Duke University Medical Center
Durham 27710

Dr. Quigless Takes on Blue Cross Blue Shield

Dr. Mr. Rose,

After the courtroom victory of Massachusetts Blue Cross Blue Shield over the Massachusetts Medical Society on the issue of Balance Billing, I am not surprised to receive your recent information packet on the COST CARE PROGRAM OF NORTH CAROLINA BLUE CROSS BLUE SHIELD. I, and perhaps many other North Carolina physicians in private practice, consider this proposal of yours to be no less than a declaration of war between your corporation and our profession.

Private practice physicians have taken the lead in the initiation of needed cost containment measures such as outpatient surgery, preadmission certification and second surgical opinions. We respond to the needs of the poor and elderly through the Medicare and Medicaid programs by providing the highest level of care at reduced rates. We willingly submit to the PRO restraints for the sake of cost containment, but fight to maintain quality of care for our patients. We staff emergency rooms and clinics where we consider our treatment of the indigent to be our duty under the Hippocratic Oath.

I cannot participate in your Cost Care Program. In fact, I find it necessary to oppose the institution of the program and I expect your corporation to suffer by my opposition. Massachusetts Blue Cross Blue Shield insures 70% of their eligible population. In the more competitive environment of our state, you only insure about 30% of those eligible. You lost the State Employee's contract. After three years your Personal Care Plan is still in the red; yet, you would essentially declare war on the physicians of this state from your obviously weak position.

You propose to tie physician fees to the Consumer Price Index at a time when our greatest economic worry is the malpractice insurance crisis which threatens to erode our financial positions as physicians to a far greater extent than inflation. You would hope to limit our income at a time when physicians finishing residencies are 28-35 years old with educational debts in the range of $100,000 or more.

Blue Cross Blue Shield was formed by physicians in the 1930's to protect the health care consumer from catastrophic health care bills. Over the years, trusting physicians allowed administrators such as yourself to become the caretakers of health care financing. Now, we are forced to retake the position of guardian of health care costs and finances from you. We are doing this by the creation of physician owned and operated Independent Practice Associations.

Mr. Rose, in my opinion, your corporation has little to offer to the doctor or the patient in the present competitive environment. Through our IPAs we physicians will regulate our own fees with no necessity for your continued assistance.

Milton D. Quigless, Jr., MD, FACS
Box 14445
Raleigh 27620

Mr. Rose responds:

I am writing in response to your invitation to comment on a letter from Dr. Milton D. Quigless, Jr. in which he expresses his views on the participating doctor program developed by Blue Cross and Blue Shield of North Carolina. I regret that he feels he cannot join other doctors and the Plan in this cost containment effort, but recognize that such is his privilege.

This program is another important step in our continuing efforts to support health care cost containment. The Plan's contribution to health care economics has evolved on two fronts: concerted actions to incorporate incentives in employee benefit programs to encourage subscribers' participation in cost containment; among institutional providers, programs designed to move inappropriate hospital-based services to ambulatory settings.

Now, we are asking doctors to join Blue Cross and Blue Shield of North Carolina voluntarily in making quality health care available at an affordable cost.

Our goals in designing the reimbursement system to be put into effect January 1, 1986 were to address employer concerns over the predictability of health care cost increases; to improve our position in a highly competitive market; and to maintain the integrity of the private health sector.

In initiating the program, we employed methods to ensure a fair and equitable method of reimbursement. Blue Cross and Blue Shield of North Carolina solicited input from practicing North Carolina doctors and from similar reimbursement programs in operation in 61 other Blue Shield Plans.

To maintain the program, we will conduct regular reviews of special needs of doctors, including malpractice insurance, through advisory groups of participating doctors, and consider appropriate changes based upon their recommendations. In addition, these groups will review the Plan's fairness in administering the participating doctor program.

Previous cost containment programs have not sacrificed the quality of care in our state. Likewise, the participating doctor program does not affect the level of benefits for health care services or limit medically necessary health care services.

The participating doctor program, as a reimbursement system, only affects the mechanism of benefit payment. Though our program seemingly shares similarities with other systems affecting the financing of health care, it must be reviewed on its own merits.

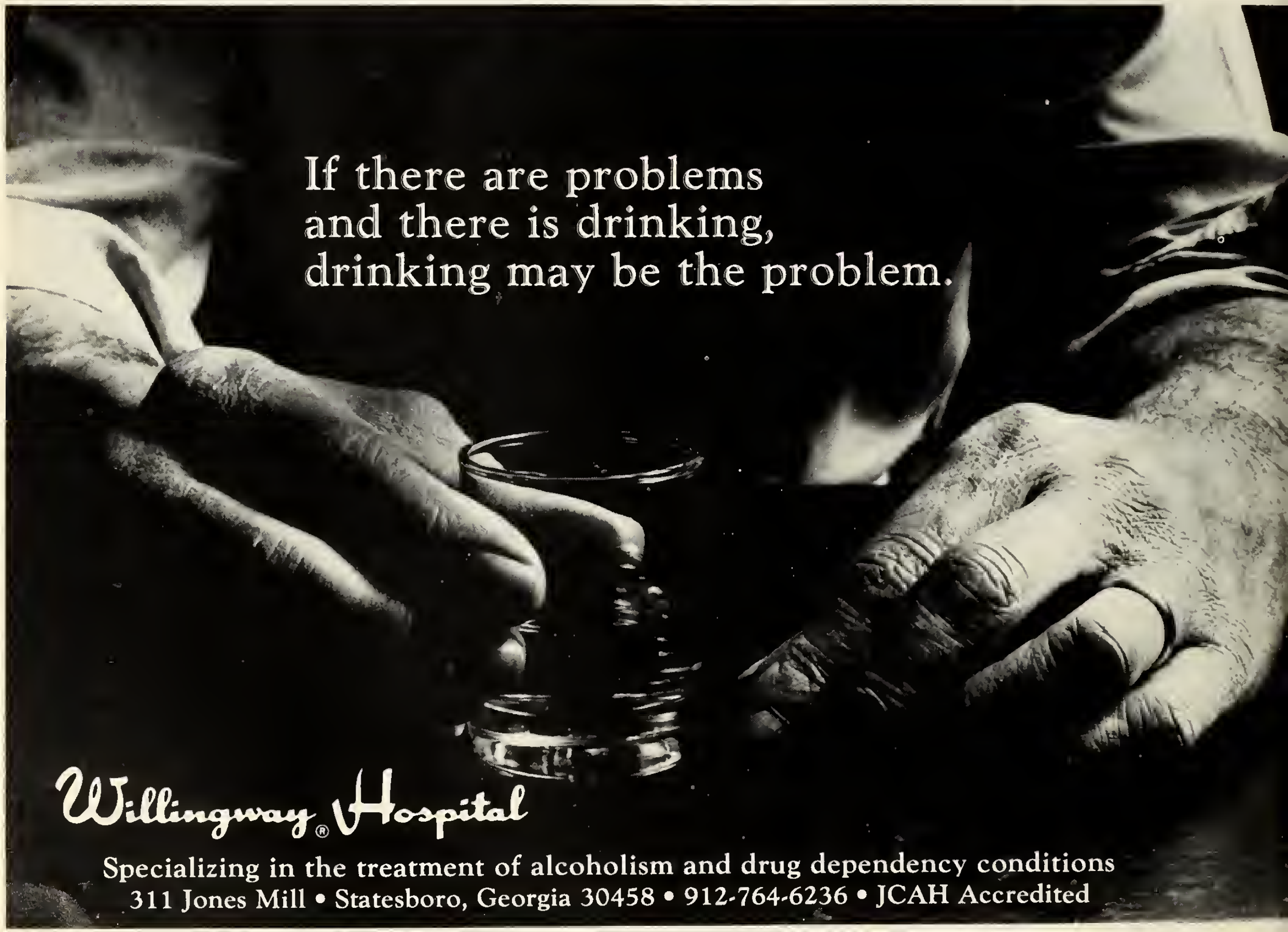
Included in those merits is the method for determining the maximum allowable. We computed this maximum at the 90th percentile of all doctors' charges. We linked fee increases to the all-items Consumer Price Index (CPI) to sustain the predictability of reimbursement increases as well as increases in rates for health insurance premiums. As noted above, special consideration will be given those factors which would impose unique costs upon doctors.

We have established a team of professional relations representatives across the state whose primary function will be to serve participating doctors by addressing any administrative concerns they may have.

As part of the Plan's contract, we provided a cancellation clause so doctors are not locked into participation. To support the success and savings potential of the program, we necessarily included a direct payment incentive for participation.

The decision to participate is an individual choice of the state's doctors. Each doctor should judge the program's impact on his or her practice. We invite North Carolina doctors to assist in making affordable health care protection available for the subscribers of Blue Cross and Blue Shield of North Carolina.

Thomas A. Rose
President, Blue Cross Blue Shield
Box 2291
Durham 27702



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